A dissertation on

A STUDY ON HIGH PREVALENCE OF METABOLIC ALTERATIONS (DYSLIPIDEMIA, DIABETES MELLITUS, HYPERURICEMIA) IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME

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M.D. GENERAL MEDICINE

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COIMBATORE MEDICAL COLLEGE,

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CERTIFICATE

This is to certify that this dissertation titled **"A STUDY ON HIGH PREVALENCE OF METABOLIC ALTERATIONS (DYSLIPIDEMIA, DIABETES MELLITUS, HYPERURICEMIA) IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME"** has been done by **Dr.SATISH.S.** under my guidance.

Further certified that this work is an original, embodying study of bonafide cases.

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DECLARATION

I Dr.SATISH.S., declare that the Dissertation titled "**A STUDY ON HIGH PREVALENCE OF METABOLIC ALTERATIONS (DYSLIPIDEMIA, DIABETES MELLITUS, HYPERURICEMIA) IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME**" Submitted to the Dr.MGR Medical University, Guindy, Chennai is an original work done by me during the academic period from May 2017- April 2018 at the Department of Medicine, Coimbatore Medical College Hospital, Coimbatore, under the guidance and direct supervision of Dr.RAVEENDRAN.M in partial fulfilment of the rules & regulations of the Dr.MGR Medical University for MD Medicine post graduate degree.

All the details of the patients, the materials and methods used are true to the best of my knowledge.

I assure that this dissertation has not been submitted to or evaluated by any other Medical University.

Dr. SATISH.S.

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Lastly, I am ever grateful to the **ALMIGHTY GOD** for always showering His blessings on me and my family

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CERTIFICATE – II

This is to certify that this dissertation work titled **A STUDY ON HIGH PREVALENCE OF METABOLIC ALTERATIONS (DYSLIPIDEMIA, DIABETES MELLITUS, HYPERURICEMIA) IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME** of the candidate DR.S.SATISH with registration Number- 201611314 for the award of M.D in the branch of General Medicine I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1% (ONE**) percentage of plagiarism in the dissertation.

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Dissertation Topic	:	**A study on the clinical correlation of the metabolic alterations (hypertriglyceridemia,diabetes mellitus and hyperuricemia) in patients with primary sjogren syndrome**

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted and you are permitted to proceed with the above Study.

24.12.16

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ABBREVIATIONS

SS – Sjogren's syndrome

AECG – American European Consensus Group

ACR – American College of Rheumatology

pSS – Primary Sjogren's Syndrome

SLE – Systemic Lupus Erythematosus

RA – Rheumatoid Arthritis

MALT – Mucosa Associated Lymphoid Tissue

CT – Computed Tomography

DM – Diabetes Mellitus

LDL - Low Density Lipoprotein

VLDL - Very Low Density Lipoprotein

HDL - High Density Lipoprotein

FBS – Fasting Blood Sugar

ALT – Alanine Transaminase

Sr – Serum

INTRODUCTION

Sjogren's syndrome is one among the common autoimmune disorders mainly involving the mucosal surfaces and the exocrine glands. Hence the major symptomatology in SS is confined to the involvement of these glands which includes dryness of the eyes- xerophthalmia, dryness of the oral cavity- xerostomia, etc. However, the clinical features of SS is not only limited to these structures but it usually multisystemic. Similarly, the exact etiology behind SS is not confined to a single entity but has been proved to be multifactorial.

The highest prevalence of SS has been found to occur in the age group of 40-50. However, it is not confined to this age distribution alone and has been reported at any age. The prevalence in females is nearly 10 times more common as that being reported among males.

The clinical course in patients who have developed SS is usually chronic and initially restricted to involve only the exocrine glands. Nearly 33%- 40% of these patients progress in due course and develop a full blown systemic illness, the most dreadful of all these being the development of Non Hodgkins lymphoma.

The prevalence and complications associated with the development of metabolic alterations during the course of the disease process of SS is not much researched. Previously, these SS patients who had evidence of

dyslipidemia or diabetes mellitus were considered to be of different syndrome complex and were named as pseudo Sjogren's Syndrome. This pseudo SS dates beck to around 1950s during which there were no proper facilities for establishing the correct etiology and linking these metabolic alterations to the disease process alone. Hence experimental models of SS were created in non obese diabetic mouse with similar exocrine disorder as in SS patients and these mouse were studied for the development of metabolic alterations.

In 2005, there were many studies done on SS and two studies quoted for the metabolic abnormalities detected in these patients. Studies done by Lodde et al have explained about the altered lipid profile noted in SS and the need for early screening of these patients. Another study conducted by Vaudu et al studied the prevalence of atherosclerosis noted in femoral and carotid doppler studies.

The management of SS patients is mainly based on the extent of systemic involvement and the development of complications. If the disease process is restricted to the exocrine glands alone, symptomatic management with topical ailments like artificial tears would suffice. Better understanding of the pathophysiology behind SS has now helped in development of drugs with target specific action namely anti CD20 and anti CD22 antibodies. These drugs are aimed to act against the surface receptors of the B lymphocytes.

AIMS

The study focuses on the metabolic alterations and various systemic involvement seen in patients diagnosed with Primary Sjogren's Syndrome.

OBJECTIVES

- To analyse the prevalence of altered lipid profile - hypercholesterolemia and hypertriglyceridemia in patients with Primary SS.
- To study the prevalence of Diabetes Mellitus in patients with Primary SS.
- To study the prevalence of hyperuricemia in patients with Primary SS.
- To study about the prevalence of various metabolic alterations and overlap with various systemic involvement in Primary SS patients.

REVIEW OF LITERATURE

Sjogren's syndrome is one of the chronic autoimmune diseases that affects many individuals within the community. Despite its wide prevalence, the exact etiology underlying sjogren's syndrome remains unclear. Sjogren's syndrome is considered to be multifactorial with genetic, environmental and hormonal factors playing a role in the pathogenesis. The disease primarily involves the exocrine glands more specifically – salivary and lacrimal glands. It is characterised by lymphocytic infiltration of the exocrine glands resulting in glandular dysfunction. The prevalence of the disease is mainly observed in middle aged women, but also being reported in children, men and elderly.

Sjogrens syndrome usually involves many systems in our body. The clinical picture usually starts with dryness of the mouth, eyes and other mucosal surfaces and in due course progresses to involve other systems manifesting as renal failure, vasculitis, interstitial lung disease, peripheral neuropathy most commonly sensory pattern and a wide range of metabolic alterations namely diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, etc.

A joint study of the American European Consensus Group (AECG) presented in 2002 the revised AECG classification criteria for SS. To date, the AECG criteria are the most widely used classification criteria (Table 1). The AECG criteria are composed of subjective symptoms (dry eyes and dry

mouth, Criterion I and II), objective signs (keratoconjunctivitis sicca and salivary gland involvement, Criterion III and V) and histopathological (Criterion IV) and serological findings (Criterion VI). Albeit the aforementioned classification criteria were developed to be used as a research tool to define homogenous groups of patients, they are broadly used in clinical practice as a diagnostic tool.

Table 1 AECG criteria for diagnosis of SS

I – Ocular symptoms (at least one of the following symptoms) • Daily, persistent troublesome dry eyes for more than 3 months • Recurrent sensation of sand or gravel in the eyes • Use of tear substitutes more than 3 times per day
II – Oral symptoms (at least one of the following symptoms) • Daily feeling of dry mouth for more than 3 months • Recurrent or persistent swollen salivary glands, as an adult • Need to drink liquids to aid swallowing dry food
III – Ocular signs (positive result from at least one of the following tests) 1. Schirmer's I test, performed without anesthesia (< 5 mm in 5 minutes) 2. Rose Bengal score or other ocular dye score (> 4, according to van Bijstervald's scoring system)
IV – Histopathology • In minor salivary glands – biopsied from normal-appearing mucosa – focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score > 1 (defined as the number of lymphocytic foci containing more than 50 lymphocytes, adjacent to normal-appearing mucous acini, per 4 mm^2 of glandular tissue
V – Salivary gland involvement (positive result from at least one of the following tests) • Unstimulated whole salivary flow (< 1.5 ml in 15 minutes) • Parotid sialography showing the presence of diffuse sialectasias • Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI – Autoantibodies (serum presence of the following autoantibodies) • Antibodies to Ro (SSA) or La (SSB), or both, in the serum
Exclusion criteria Past head and neck radiation treatment; Hepatitis C infection; Acquired immunodeficiency syndrome; Pre-existing lymphoma or sarcoidosis; Graft versus host disease; Use of anticholinergic drugs

Due to the emergence of biologic agents, the American College of Rheumatology (ACR) proposed new classification criteria for SS, based merely on objective tests (Table 2).

Table 2. ACR criteria for diagnosis of SS

Proposed classification criteria for SS : ACR (2012)

- 1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer 1:320)
- 2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score 1 focus/4 mm^2
- 3. Keratoconjunctivitis sicca with ocular staining score 3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)

Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

Head / Neck Radiation
HCV Inf
AIDS
Sarcoidosis
Amyloidosis
GVHD

CLASSIFICATION

It is generally classified into two types namely Primary Sjogren's Syndrome and Secondary SS. Primary SS usually occurs in the absence of other autoimmune diseases and is characterized by keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth), collectively called the sicca syndrome. In contrast, secondary SS occurs in pre-existing autoimmune diseases like rheumatoid arthritis , systemic lupus erythematosus, scleroderma , etc.

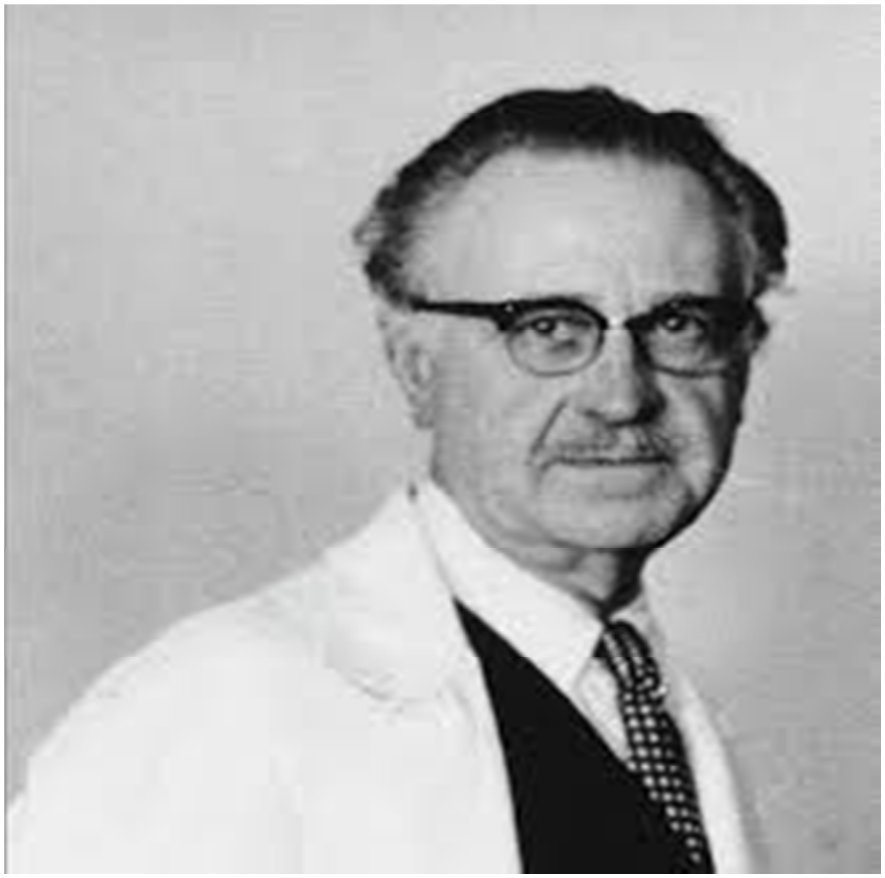
HISTORY

Sjogren's syndrome was first studied in detail by a Swedish ophthalmologist, Henrik Sjogren and hence the term Sjogren's Syndrome was coined. The research work regarding SS and associated conditions dates back to nearly the 14^{th} century. The association of dry eyes and dry mouth was described by Hadden in 1888 and the coincidence of lacrimal and salivary gland enlargement by Mikulicz in 1888. The correlation of systemic nature of the disease with ocular dryness was postulated by 1925. Although many such milestones in SS has been achieved, it was not until 1933 that a full description of the condition was given by the Swedish ophthalmologist Henrik Sjogren.

Henrick Sjögren 1899-1987 Sweden 1930-As ophthalmology resident discover women with rheumatism and corneal abrasions who could not produce tears when crying and could not dissolve a lump of sugar in their mouths. 1933-Published his thesis paper on Keratoconjunctivitis Sicca, describing 15 women with lacrimal gland dysfunction leading to ulcerative

lesions of the eyes. He was not well received, did not acquire Docenti (Academic PhD). 1951-Sjögren published a series of papers describing 80 patients with the syndrome, in which the majority had arthritis. Sjögren's syndrome was then recognized in literature.

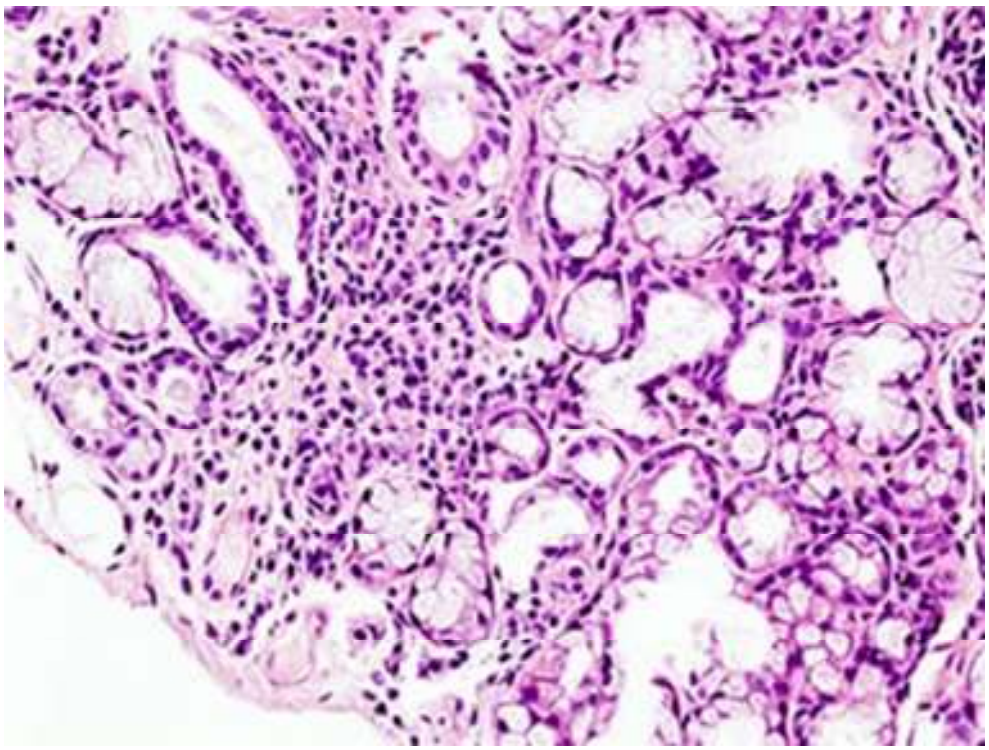
FIGURE 1. Henrick Sjogren



In the meanwhile, there was a gross confusion regarding the relationship between SS and the disease reported by Mikulicz. In 1927, Schaffer and Jacobson together solved this problem by dividing into Mikulicz's disease and Mikulicz's syndrome. Mikulicz's disease was named after the disease being reported by Mikulicz, characterised by enlargement of the lacrimal and parotid glands due to lymphocytic infiltration of unknown

etiology. Mikulicz's syndrome was termed conditions involving enlargement of the same glands as a result of systemic diseases like leukemia, lymphosarcoma, tuberculosis and sarcoidosis. It was only in 1953, Morgan and Castleman concluded that Mikulicz disease and SS are identical, sharing the same histopathological features. It was reported that the histopathological changes of lymphocytic infiltration, acinar atrophy and cystic or solid duct alterations were seen in both diffusely enlarged salivary glands of patients with xerostomia as well as in localized salivary gland nodules of patients who were otherwise asymptomatic. This was termed as benign lymphoepithelial lesion. Similar findings noted in symptomatic individuals was regarded as SS.

FIGURE 2. Histopathology of SS



As years passed by, further advancements in both clinical and pathological diagnosis were brought about. In 1965, Bloch and Buchanan postulated a triad for the diagnosis of SS namely- keratoconjunctivitis sicca , xerostomia and a connective tissue disease most frequently rheumatoid arthritis. The diagnosis of SS requires atleast two of the above triad. It has been recognized universally and forms a milestone for the development of current postulates for diagnosing Systemic Sclerosis.

EPIDEMIOLOGY

Sjögren's syndrome (SS) is a common systemic disease, second to rheumatoid arthritis (RA), with a prevalence of 6 (95% CI: 4.7 to 7.9) cases per 100,000 inhabitants in the total population. Although commonly prevalent among middle aged females, the incidence of juvenile SS is on the raise in recent years. The male to female ratio of occurrence of SS has been found to be 1:9. The prevalence of SS in females accounts to about 6.9 cases per 100000 whereas the prevalence in males accounts to 0.5 per 100000 population. However there appears to be a mild difference in the prevalence rate depending on the criteria used for diagnosis.

The mean age of onset of sjogren's syndrome is in the age group of 40-50 years. However, it has also been reported in the 6^{th} to 7^{th} decade. This is especially true in case of primary sjogren's syndrome where nearly 40 per cent cases have been reported above 65 years of age. There are been multiple factors which are attributed to the development of SS in the elderly population. The

commonly noted factors correlating with higher incidence of SS includes physiological reduction in the salivary gland function with age, diabetes, multiple drug intake, etc. The incidence of pSS in children is extremely rare where the age of onset is usually from 3 to 17 years and female to male ratio being 5:1.

SS commonly affects the exocrine glands, in particular the salivary and lacrimal glands, resulting in a sensation of dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). SS can be distinguished in primary Sjögren's syndrome (pSS), in case no other autoimmune disease is present, and secondary Sjögren's syndrome (sSS), in case additional connective tissue diseases are present, such as RA, systemic lupus erythematosus (SLE), scleroderma and mixed connective tissue disease.

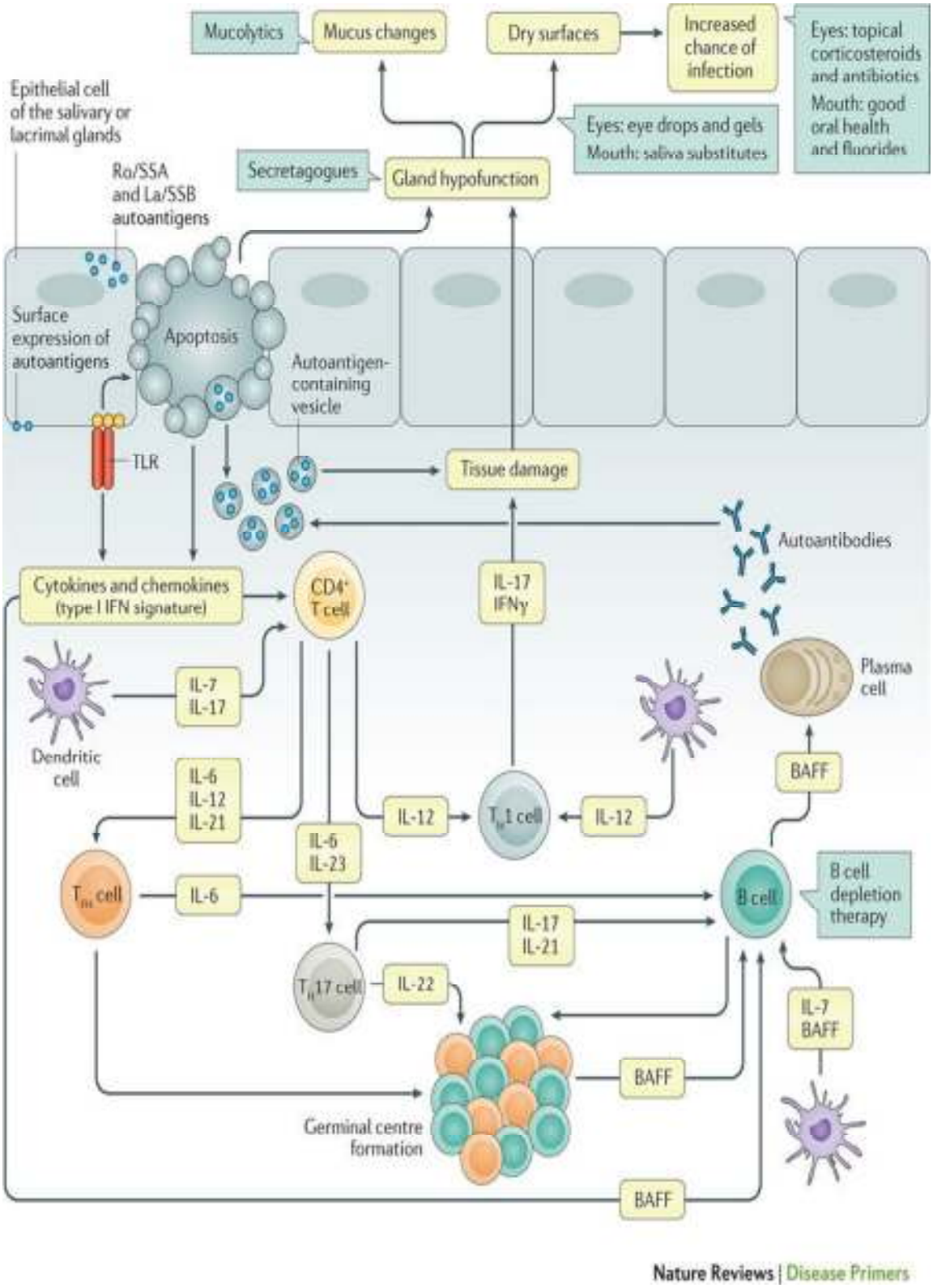
Although the exact pathogenetic mechanism has not been fully elucidated, in patients with SS both the minor and major salivary glands as well as the lacrimal glands are characteristically infiltrated by mononuclear lymphoid cells. The classic glandular lesion is composed of a periductal lymphoid infiltrate of T and B lymphocytes, whose distribution may vary according to lesion severity. The periductal localization of the infiltrate emphasizes the critical role of the epithelium in the development of the disease. In addition to lymphoid cells, also a wide variety of non-lymphoid cells can be found within the infiltrate; in fact, all elements responsible to carry out (auto)immune responses may be present.

A central role in the pathogenesis of SS is attributed to B-cells, which are found to be hyperactive. In line with this finding, patients with pSS have an increased risk of developing lymphoproliferative diseases, which is about 3.9% during the first 5 years, 11% at 15 years and 16% after 25 years of diagnosis.

ETIOPATHOGENESIS

There has been a long drawn debate about the pathogenesis of SS. Recent evidences are supportive towards the mainstay involvement of B lymphocytes in the autoimmune process behind SS. T lymphocytes are also involved in the lymphocytic inflammation of the exocrine glands.

FIGURE 3. Etiopathogenesis of SS



In pSS, germinal centers are reported in the epithelium of non-lymphoid tissues such as the salivary glands. The formation of germinal centers is probably important in the pathogenesis of pSS due to promotion of chronic stimulation and activation (by follicular T helper cells) of B cells. Patients with pSS often present with high levels of serum IgA and/or IgG. Hyperglobulinemia may lead to the formation of immune complexes with the potential to precipitate in major organs leading to (irreversible) damage.

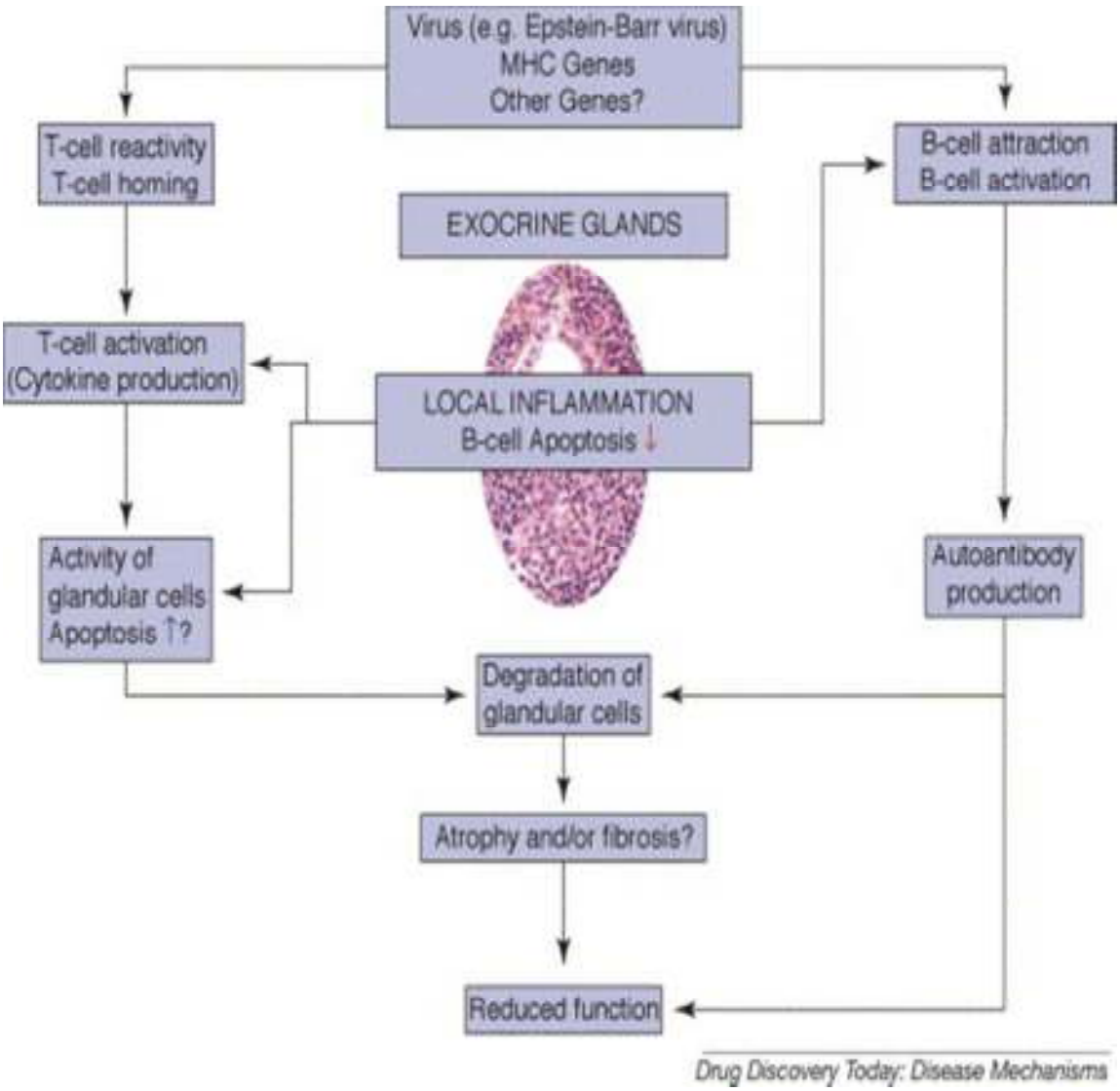
In addition, the presence of autoantibodies (anti-Ro52, anti-Ro60 and anti-La) is included in the diagnostic criteria for pSS. The presence of these autoantibodies is associated with early onset disease, parotid gland enlargement, extraglandular manifestations and lymphocytic glandular infiltration. In sum, it remains unclear how these changes in the adaptive immune system lead to the clinical manifestations of pSS. The traditional view that chronic inflammation results in tissue destruction of the exocrine glands will only partially contribute to the pathogenesis of pSS. There is a poor correlation between the amount of damage observed in tissue biopsies and the measured decrease in fluid production, as the reduction in salivary production is often larger than expected from both clinical and histological appearance.

Studies done by Mahendranath et al postulated few points regarding the pathogenesis of SS. An increased association with HLA-Dw3(DR3) and DR5 has been reported. Patients with antibodies to Ro and La have an increased frequency of HLA DR313. In contrast a study14 among secondary Sjögren's syndrome (most with SLE or RA) only DR5 was increased. A viral

aetiological factor has been considered as playing an important role because the salivary glands are known to be the site of latency for various viruses. The possible mechanisms by which viruses can induce tolerance bypass, include polyclonal activation of B cells, molecular mimicry between viral epitopes and autoantigens, modified self, idiotypic netware perturbation, exposure of so called “hidden antigens” and direct toxic effects of viruses on target cells. All these mechanisms may be applicable to Sjögren’s syndrome.

Currently, the pathogenesis behind sjogren’s syndrome is considered to be due to alteration in the immunoregulation in which there is a lymphocyte mediated destruction of the exocrine glands. This in turn will culminate in diminished or absent glandular secretion and mucosal dryness. There are mainly two different variants of pathological appearance in the salivary glands namely : the lymphoepithelial lesion, occurring in the major salivary glands, especially the parotid glands and focal lymphocytic sialadenitis in the minor salivary glands.

FIGURE 5. Immune mediated degradation of exocrine glands



The proliferation of intraparotid lymphoid tissue and infiltration of lymphocytes aggregating around the salivary glands is seen in lymphoepithelial lesion. The glandular epithelium is being replaced by proliferating cells and may result in clinically significant glandular enlargement. This in turn progresses to metaplastic and hyperplastic ductal epithelium obliterating the ductal lumen followed by acinar atrophy. These pathological changes aggravate until the involved salivary gland becomes totally effaced by lymphocytes,

leaving only residual deformed ducts, which are called epimyoepithelial islands.

In 4-5 % cases, there occurs malignant transformation of the lymphocytic infiltrates, leading to the development of malignant lymphoma. Having close similarity with MALT tissue, these lymphomas of the salivary gland are termed as lymphomas of MALT-type. The only difference from other lymphomas is that they resemble a chronic inflammatory process and remain localized for long periods and their clinical course is relatively indolent.

Focal lymphocytic sialadenitis is the characteristic feature of minor salivary glands. This is characterised by primary lymphocytic infiltrate into the glands and is characterized by focal aggregates of 50 or more lymphocytes adjacent to normal appearing acini, present in all or most of the glands.

Defining in immunological terms, the prevailing abnormality is polyclonal B cell hyperactivity and alterations in the immunoregulatory T-lymphocytes. The presence of polyclonal hyperglobulinemia in the serum and the presence of several antibodies denotes B-lymphocyte hyperactivity.

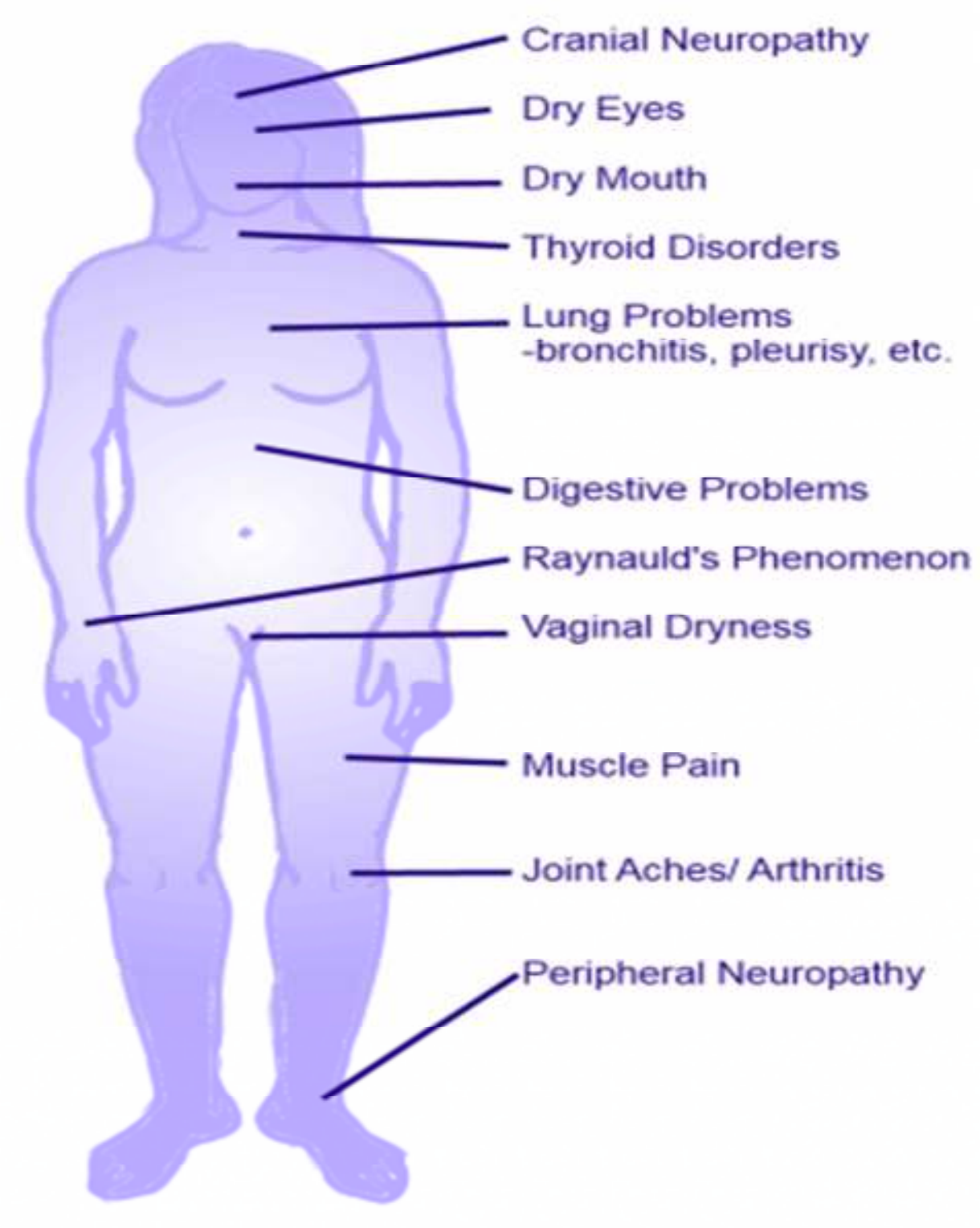
There are many theories postulated for the explanation of the etiology of this immune variation among individuals. One such theory is genetic abnormality of the immune system characterised by either spontaneous B-lymphocyte activation or excessive T-helper cell function or decreased T-suppressor cell function causes B-lymphocyte overactivation and production of

antibodies. Second possibility postulated was antigenic challenge, the acquired antigenic stimulus secondary to a viral disease that alters surface autoantigens leading to B cell activation and production of autoantibodies. The third postulate is combining the above two theories, in which there is interaction of an acquired exogenous stimulus with a certain genetic susceptibility. The interaction of sex steroid hormones and abnormal apoptosis are the other mechanisms proposed to induce initial autoimmune response.

CLINICAL FEATURES

The clinical presentation for pSS is not uniform, as many patients have various degrees of systemic involvement at the time of presentation.

FIGURE 5. Clinical features of SS



The symptoms of pSS can be divided into three groups,

(1) sicca syndrome

(2) generalized symptoms and

(3) systemic involvement

SICCA SYNDROME

Sicca syndrome is dryness of the mucous membrane of the eyes (xerophthalmia) , oral cavity (xerostomia) and in females with dryness of vaginal mucosa. The American European classification criteria (AECG) of 2002 for pSS includes this syndrome complex. The positive predictive value for this current criteria has been found to be 61-83% and the negative predictive value is between 96-99% when compared with previous classification criteria of 1986.

Candidiasis (39%), caries tooth (59%) and periodontal disease are some of the complications of xerostomia in the long term. The tongue is usually smooth with fissures and atrophy of the filiform papillae. There is always a difficulty in tolerating conventional dentures in edentulous patients where implant retained prostheses seems to be better tolerable. Sialography is a radio-contrast method of assessing anatomical changes in the salivary duct system.

Photosensitivity, foreign body sensation, corneal epithelium destruction and ocular infections are commonly associated with xerophthalmia.

Chronic and persistent irritation is the only frequent complaint of these patients. They are usually unable to tolerate smoke, air drafts or light.

Hoarseness of voice, dry cough, dryness of the skin and, in woman, dyspareunia due to dryness of the vaginal mucosa commonly occur. There has been noted a significant reduction in the quality of life in SS patients with sicca syndrome alone without autoimmune features.

GENERAL SYMPTOMS

The most prevalent general symptom is fatigue, occurring in up to 70-80% of pSS patients. Fatigue in pSS has been well studied using the multidimensional fatigue inventory (MFI) on which pSS patients scores were two-fold worse on all dimensions as compared to healthy controls. In addition, chronic pain is often seen in pSS due to accompanying fibromyalgia and/or polyarthralgia. Depression and anxiety are also more common in pSS patients compared to healthy controls. A study conducted by Tim and Martin et al showed that 47% of the working age pSS patients received disability compensation, because they were considered to be (partially) unfit for work. The same study also reports that significantly more patients with the following demographic/disease characteristics receive disability compensation: male patients, patients with a high educational level, an increasing number of systemic manifestations and/or the use of artificial saliva and/or HCQ.

SYSTEMIC MANIFESTATIONS

The characteristic manifestations of sjogrens syndrome in various individual organ systems have been enlisted below :

1. MUSCULOSKELETAL SYSTEM : Studies done by Maralampos et al revealed that most patients with SS suffer from chronic fatigue. Arthralgia has been reported in 90% of patients whereas true arthritis is seen in 10% only. About 10-12% of patients develop fibromyalgia like symptoms. Arthralgia, myalgia and morning stiffness have also been reported., but frank myositis is uncommon. Non erosive arthritis and rheumatoid arthritis like symmetrical joint involvement also occurs. Intermittent inflammatory synovitis, non erosive inflammatory arthritis and inflammatory myositis is also seen in 50% of individuals.

2. RESPIRATORY SYSTEM : Involvement of the respiratory tract is more commonly reported in Primary SS, but it is of less clinical significance. Nearly 50% of the patients show evidence of interstitial lung involvement in chest radiography. The presence of bronchial or peribronchial thickening, bronchial lymphoid infiltrates and follicular bronchiolitis in high resolution CT is usually diagnostic. The suspicion of lymphoma should be held in mind when there is hilar or mediastinal lymphadenopathy or lung nodules. Primary SS may sometimes be associated with pleural effusion.

3. GASTROINTESTINAL SYSTEM : Dysphagia may result from dryness of the pharynx and esophagus. Chronic atrophic gastritis and lymphocytic infiltrates of the gastric mucosa may be observed. The prevalence of H.pylori infection has been found to be higher in SS patients. This has contributed to the gastric mucosa-associated lymphoid tissue lymphomas. Liver involvement in primary SS is rare (5%) and is usually subclinical. Small bowel biopsy may reveal celiac-like disease in 15% patients with primary SS. Sicca manifestations are seen in nearly 50-80 % patients with primary biliary cirrhosis. Subclinical pancreatic involvement is common and associated with increased serum amylase levels in 25% of patients.

4. EXCRETORY SYSTEM : Renal involvement is seen in about 6% of patients with primary SS. The presentation of renal injury is either as interstitial nephritis or glomerulonephritis. Interstitial nephritis is subclinical and follows a benign course. Immune complex glomerulonephritis (membrano proliferative or mesangio proliferative) is associated with cryoglobulinemia and hypocomplementemia and may progress on to develop chronic renal insufficiency. Subclinical Distal Renal Tubular Acidosis is reported in one third of the patients. They usually present with hypokalemic muscular weakness, recurrent renal calculi which can lead on to nephrocalcinosis if untreated. Lymphocytic infiltrative lesions result in interstitial nephritis usually presenting with suprapubic pain and frequent micturition.

5. VASCULAR MANIFESTATIONS : Many studies reveal that Raynaud's phenomenon is seen in 30-40% patients. Nailfold capillaroscopy may show scleroderma like lesions in primary SS with anti-centromere antibodies. Small vessel vasculitis is seen in 20-30% of patients, which usually presents with palpable purpura, petechial rash, urticaria or annular erythema of the face or trunk. A rare phenomenon noted is systemic necrotizing vasculitis with visceral involvement affecting kidney, lungs or gastrointestinal tract.

6. NEUROENDOCRINE AND PSYCHIATRIC MANIFESTATIONS : Entrapment syndrome, peripheral sensory or sensorimotor polyneuropathy and/or mononeuritis multiplex may occur. There have been case reports of hemiparesis, seizures, cerebellar defects and transverse myelopathy in primary SS. The development of anti-m3 muscarinic antibodies may result in autonomic dysfunction. Anxiety, depressed mood and personality disorders are observed. Hypoactivity of the hypothalamo pituitary adrenal axis has been noted.

7. OTHER MANIFESTATIONS : Thyroid abnormalities in the form of increased TSH levels and anti thyroid peroxidase antibodies have been reported in few studies. But there has been no clear cut clinical evidence of autoimmune thyroiditis in these individuals. Sensorineural hearing loss has been reported to have four fold increased prevalence in SS patients. There has been no supporting studies about the development of infertility in SS patients, but insufficient vaginal lubrication may result in dyspareunia due to atrophic vaginitis and perivascular infiltration. Elevated erythrocyte

sedimentation rate has been reported in almost 90% of the SS patients and it has been attributed to the autoimmune process.

8. METABOLIC DERANGEMENTS : The first common metabolic alteration with high prevalence in SS patients is hypercholesterolemia as reported by studies conducted by Alphonso Vargas et al. further studies done on SS patients were based on the concept that this elevated serum cholesterol was one among the factors quoted in the pathophysiology of SS. In studies conducted by Izhumti et al, the level of salivary glandular functioning was linked with the serum cholesterol levels.

Hypertriglyceridemia has been reported in nearly 25% of SS patients. A comparative study was conducted to analyse the difference between the prevalence of Raynaud's phenomenon, vasculitis and the involvement of various organ systems namely liver and kidneys. The result of this study was that there was a higher prevalence of these complications in SS patients with hypertriglyceridemia. However , these studies also revealed that there was no correlation between the seropositivity for anti Ro and anti La antibodies with these metabolic alterations.

The second most common metabolic alteration is diabetes mellitus with an incidence of 10%. There was significant correlation between the prevalence of Diabetes Mellitus with other extraglandular manifestations of SS. This further directs towards the search for similar etiopathogenetic factors which might worsen or initiate the inflammatory process in SS patients. This

inflammatory process will in turn lead on to vascular damage presenting as Raynaud's phenomenon, cutaneous vasculitis and glomerulonephritis. Studies done by Antonelli et al have further demonstrated the role of cryoglobulinemia in the pathogenesis of vasculitis in patients with concomitant prevalence of SS and Diabetes mellitus.

Hyperuricemia is another metabolic derangement noted in higher frequency in SS. Several studies regarding the prevalence of hyperuricemia in SS have shown that the prevalence was lower in females than males. The mean age at which hyperuricemia occurs in SS is also higher than usual.

The incidence of hypothyroidism is comparatively on the higher side in patients with sjogren's syndrome. Another point of interest is that, autoimmune thyroiditis presenting as subclinical hypothyroidism is much more common than clinically diagnosed hypothyroidism. Hence it is mandatory to screen every individual with sjogren's syndrome for thyroid dysfunction.

The coexistence of two or more metabolic alterations has been increasingly reported. With respect to the immunological profile, no significant differences were found except for a lower frequency of positive anti-Ro/SSA. The age at SS diagnosis and presence of Raynaud's phenomenon were significant independent variables in the multivariate analysis. The correlation between the treatment with various drugs with the prevalence of these metabolic alterations has not been established.

Hence the metabolic profile doesn't vary with the treatment given to SS patients.

9. LYMPHOMAS- MALT : Patients with Sjogren's syndrome have 44 times increased risk of developing lymphoma as compared to general population. Most of the lymphomas are low grade B cell lymphomas of the mucosa-associated lymphoid tissue (MALT) type and roost occur within the salivary glands. The earliest diagnostic feature of this lesion is a proliferation of centrocyte like cells around epithelial islands. These cells meet the criteria for a lymphoid neoplasm since they show light and heavy chain monoclonality, but the monoclonality may antedate the development of lymphoma by many years.

DIAGNOSIS

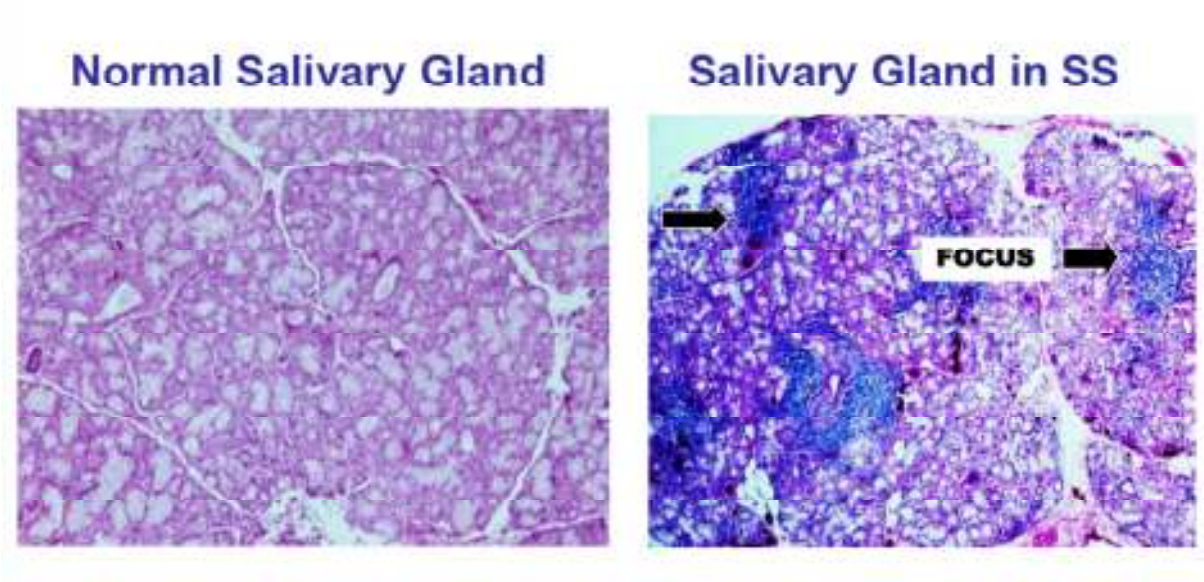
Preliminary diagnosis based on the revised AECG criteria is as follows :

I – Ocular symptoms (at least one of the following symptoms) • Daily, persistent troublesome dry eyes for more than 3 months • Recurrent sensation of sand or gravel in the eyes • Use of tear substitutes more than 3 times per day
II – Oral symptoms (at least one of the following symptoms) • Daily feeling of dry mouth for more than 3 months • Recurrent or persistent swollen salivary glands, as an adult • Need to drink liquids to aid swallowing dry food
III – Ocular signs (positive result from at least one of the following tests) 1. Schirmer's I test, performed without anesthesia (< 5 mm in 5 minutes) 2. Rose Bengal score or other ocular dye score (> 4, according to van Bijstervald's scoring system)
IV – Histopathology • In minor salivary glands – biopsied from normal-appearing mucosa – focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score > 1 (defined as the number of lymphocytic foci containing more than 50 lymphocytes, adjacent to normal-appearing mucous acini, per 4 mm^2 of glandular tissue
V – Salivary gland involvement (positive result from at least one of the following tests) • Unstimulated whole salivary flow (< 1.5 ml in 15 minutes) • Parotid sialography showing the presence of diffuse sialectasias • Salivary scintigraphy showing delayed uptake, reduced concentration, and/or delayed excretion of tracer
VI – Autoantibodies (serum presence of the following autoantibodies) • Antibodies to Ro (SSA) or La (SSB), or both, in the serum
Exclusion criteria Past head and neck radiation treatment; Hepatitis C infection; Acquired immunodeficiency syndrome; Pre-existing lymphoma or sarcoidosis; Graft versus host disease; Use of anticholinergic drugs

INVESTIGATIONS

1. SEROLOGY : Detection of anti Ro/SSA and anti La/SSB , as included in the Revised International criteria for diagnosis of SS, plays a prime role in diagnosis of SS. By standard gel precipitation method, nearly 40-60% patients with SS have been found to be positive for anti-Ro and 25-40% patients have positivity for anti-La antibodies. The presence of other autoantibodies such as antinuclear antibodies or rheumatoid factor may be useful in detecting the cause of Secondary SS. Circulating immune complexes, hypergammaglobulinemia and autoantibodies directed against various organ specific and non-organ specific autoantigens are due to polyclonal B cell activation. Pregnant mothers positive for such antibodies are at increased risk of foetal heart blocks. Alpha fondrin is the recently postulated auto antibody in primary SS.
2. BIOPSY : Lip biopsy is usually done to add on the diagnosis of SS. The biopsy specimen demonstrates infiltration of the minor salivary glands by B and T lymphocytes. The involvement of more than 50% of the acini and adjacent ducts with aggregation of lymphocytes and plasma cells is the characteristic lesion described. Although lip biopsy is not an essential entity for the diagnosis, it provides additional information for understanding the pathogenesis behind SS. The specificity of the test is increased by using it along with sialometry.

FIGURE 6. Lip biopsy histological view



3. TESTS FOR XEROSTOMIA : The various tests for xerophthalmia are as follows

    a) Sialometry

    b) Sialography

    c) Scintigraphic isotope scanning

FIGURE 7. Sialography showing cherry blossom appearance

4. TESTS FOR XEROPHTHALMIA : Schimer's test , Rose Bengal staining and Tear drop test . These tests are more sensitive but less specific for diagnosis of primary SS.

Schimers test: A 30mm strip is inserted in the lower palpebral conjunctiva . Wetting of less than 5mm is considered as positive for dry eye.

Rose Bengal test : Slit lamp examination of the cornea following rose Bengal stain(an aniline compound) reveals punctate pattern of filamentary keratitis.

Tear drop test : After instilling fluoroscein dye into the eye the time interval between the last blink and appearance of dark non fluorescent areas in the tear film is estimated . Rapid break up of the tear film indicates abnormality in the lipid or mucin layer of tear drop.

FIGURE 8. Tests for Xerophthalmia

TREATMENT

The prevention and treatment of sicca syndrome and its constitutional symptoms remains the main modality of treatment. These objectives can generally be accomplished without rheumatology consultation, because Sjogren's syndrome is a chronic disease with a broad clinical spectrum, patients should also be regularly followed for significant functional deterioration and evidence of disease complications such as extra glandular involvement or lymphoma; if these occur, specialty consultation is appropriate.

Lubrication for dry eye with artificial tear drops and ocular ointment more frequently as needed even as early as hourly once. Oral pilocarpine 5 mg four times daily has been shown to reduce the ocular symptoms of Sjogren's syndrome without serious adverse effects6,7. Topical administration of cyclosporine 0.05% has been shown to be moderately effective in a placebo-controlled clinical trial and is now FDA approved for keratoconjunctivitis sicca. Punctual cauterisation has been proved to be useful in cases of severely dry eyes. In cases of perforation, corneal transplantation can be done.

Treatment of xerostomia usually is by increasing the salivary outflow by sugar free highly flavoured lozenges. Maintainence of good oral hygiene after meals helps to prevent dental infections. Topical treatment with stannous fluoride enhances dental mineralization and retards damage to tooth surfaces. Symptomatic relief can been achieved by use of muscarinic agonists

like pilocarpine and cevimeline. These agents act on the M1 and M3 muscarinic receptors in the salivary glands, which in turn will increase the secretory function. Side effects such as flushing, headache, and sweating are uncomfortable but usually mild.

The following medications are being used in the treatment of SS based on the system involved :

1. NSAIDS : Arthralgia and other joint symptoms are usually treated with non steroidal anti inflammatory agents. Side effects may include indigestion and stomach bleeding.

2. CORTICOSTEROIDS : They usually reduce the inflammation and provide symptomatic relief of joint symptoms. Long term administration of corticosteroids have been found to be of reduced efficacy. This will result in untoward adverse effects namely easy bruising, thinning of bones, cataracts, weight gain, round face, diabetes and high blood pressure.

3. HYDROXYCHLOROQUINE : This is mainly used at a dosage of 200-400 mg/day, only when patients present with joint symptoms. It is usually ineffective in treatment of sicca symptoms.

4. IMMUNOSUPPRESANTS : These medications, such as cyclophosphamide, methotrexate, mycophenolate and azathioprine, suppress the immune system and helps in control of symptoms.

5. TNF alpha INHIBITORS : It is usually given as three separate doses at 0,2 and 6 weeks. Infliximab is used at a dose of 3mg/kg at 0,2 and 6 weeks. Studies done by Karteek et al have shown that there is statistically significant improvement in patients with SS when treated with TNF alpha inhibitors. These patients have been found to be clinically, functionally and symptomatically better even after administration of a singles course of these drugs. This proves the efficacy of these drugs in SS.

6. OTHER MEASURES : High dose intravenous immunoglobulin and plasma exchange has been used but it is proved to provide less clinical and symptomatic relief.

MATERIALS AND METHODOLOGY

STUDY DESIGN : Comparative Cross Sectional Study

INCLUSION CRITERIA :

1. Patients with Primary Sjogren's Syndrome in the age group between 20-50 years of age.
2. Both male and female population

EXCLUSION CRITERIA

1. Patients who have attained menopause
2. Patients with family history of Diabetes Mellitus
3. Previous or present history of thyroid disease
4. Patients who did not give consent
5. Patients who are already on steroid therapy for other diseases
6. Patients with history of smoking or alcohol intake

METHODOLOGY

This is a Comparative Cross Sectional Study of about 30 cases of Primary Sjogren's Syndrome who attended Rheumatology out patient department or admitted in medical ward in Coimbatore Medical College Hospital during the period of MAY 2017 to APRIL 2018. These 30 patients were selected based on the above mentioned inclusion and exclusion criteria.

Patients who are diagnosed to have Primary Sjogren's Syndrome according to the AECG guidelines are selected and screened for the presence of various metabolic abnormalities like dyslipidemia, Diabetes Mellitus, hyperuricemia, etc. The overlap of these metabolic derangements with various systemic manifestations of SS has also been compared in the study.

SOURCE OF SUBJECTS

Patients diagnosed to have Primary SS attending our Rheumatology opd or admitted in medical wards in Coimbatore Medical College Hospital are included in the study.

SOURCE OF DATA

The data collected by the principle investigator from patients with Primary SS either in opd or wards in Coimbatore Medical College Hospital.

DURATION OF STUDY

May 2017 to April 2018

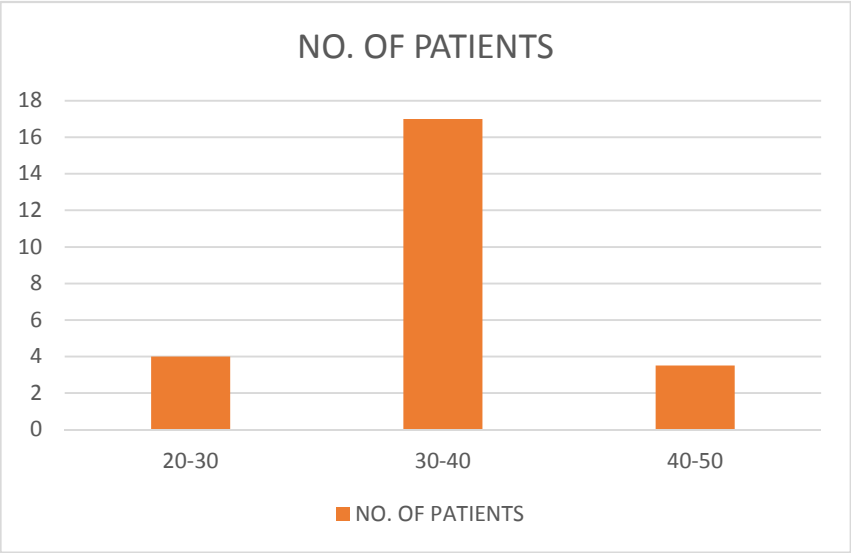
OBSERVATION AND RESULTS

AGE DISTRIBUTION

Table 3 illustrates age distribution of the study population

AGE	NUMBER OF PATIENTS
20-30	4
30-40	17
40-50	9

CHART 1 showing age distribution of the study group



CONCLUSION :- From our study, the prevalence of SS is more in the 4th decade (30-40 years). This correlates with previous studies and is also confirmed to be statistically significant.

Table 4 showing sex distribution of the study population

Gender

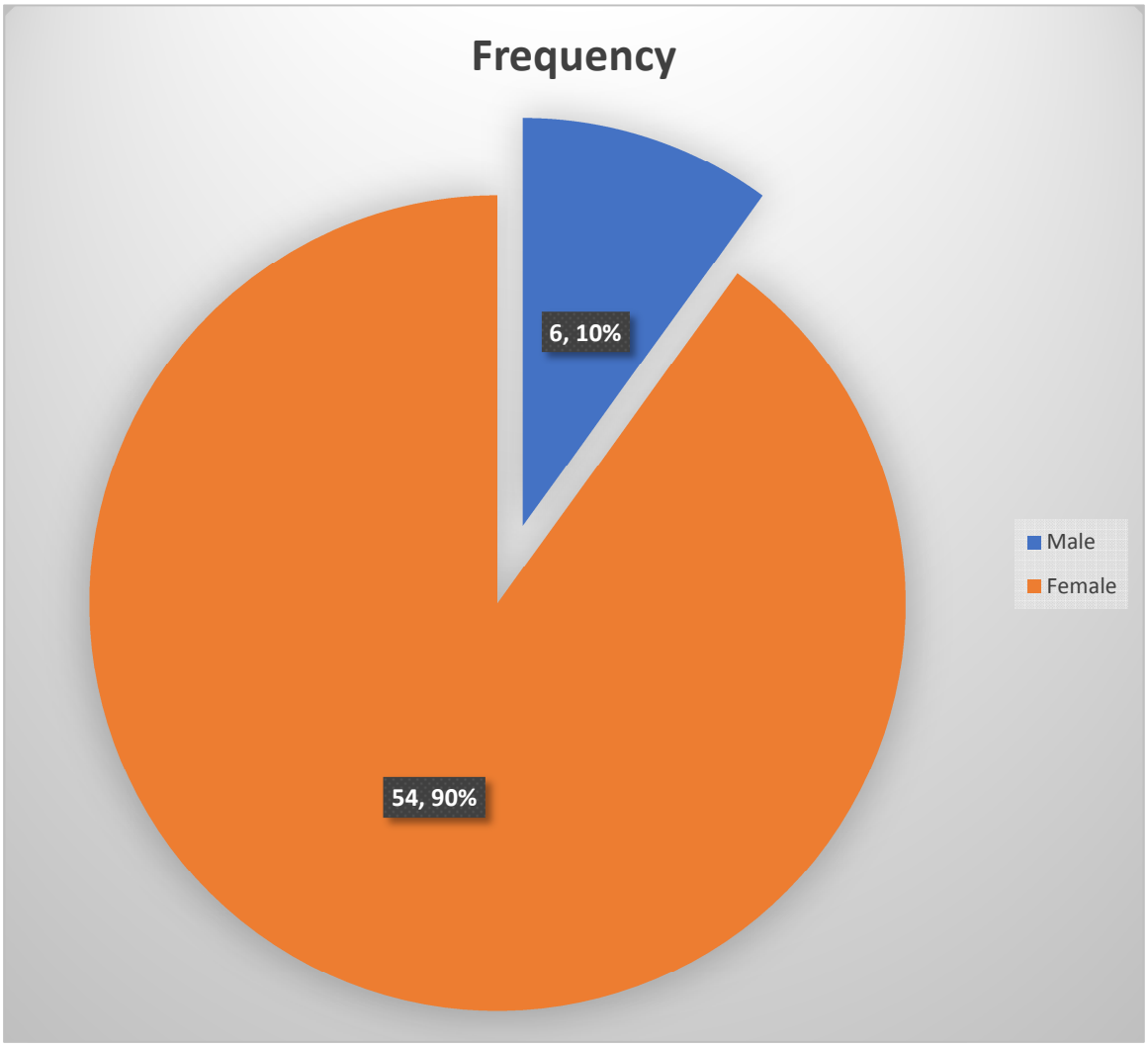
	Observed N	Expected N	Residual
Male	6	30.0	-24.0
Female	54	30.0	24.0
Total	60		

Test Statistics

	gender	Normality
Chi-Square	38.400[a]	.000[a]
Df	1	1
Asymp. Sig.	.000	1.000

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 30.0.

CHART 2 showing sex distribution of the study population



CONCLUSION :- Female patients are much greater in number than the male patients. Hence the prevalence of SS is more common females than males.

Table No 5a shows the level of Serum Cholesterol among the Control and SS Patients

Normality	Mean	N	Std. Deviation
Normal	163.8333	30	42.35408
SS	214.1000	30	55.13141
Total	188.9667	60	54.93724

Table No 5b Shows the Summary of *ANOVA* for the scores of Control and SS patients in Serum Cholesterol

			Sum of Squares	Df	Mean Square	F	Sig.
sr cholestrol * Normality	Between Groups		37901.06	1	37901.06	15.683	.000
	Within Groups		140166.86	58	2416.670		
	Total		178067.93	59			

CHART 3 Showing prevalence of hypercholesterolemia

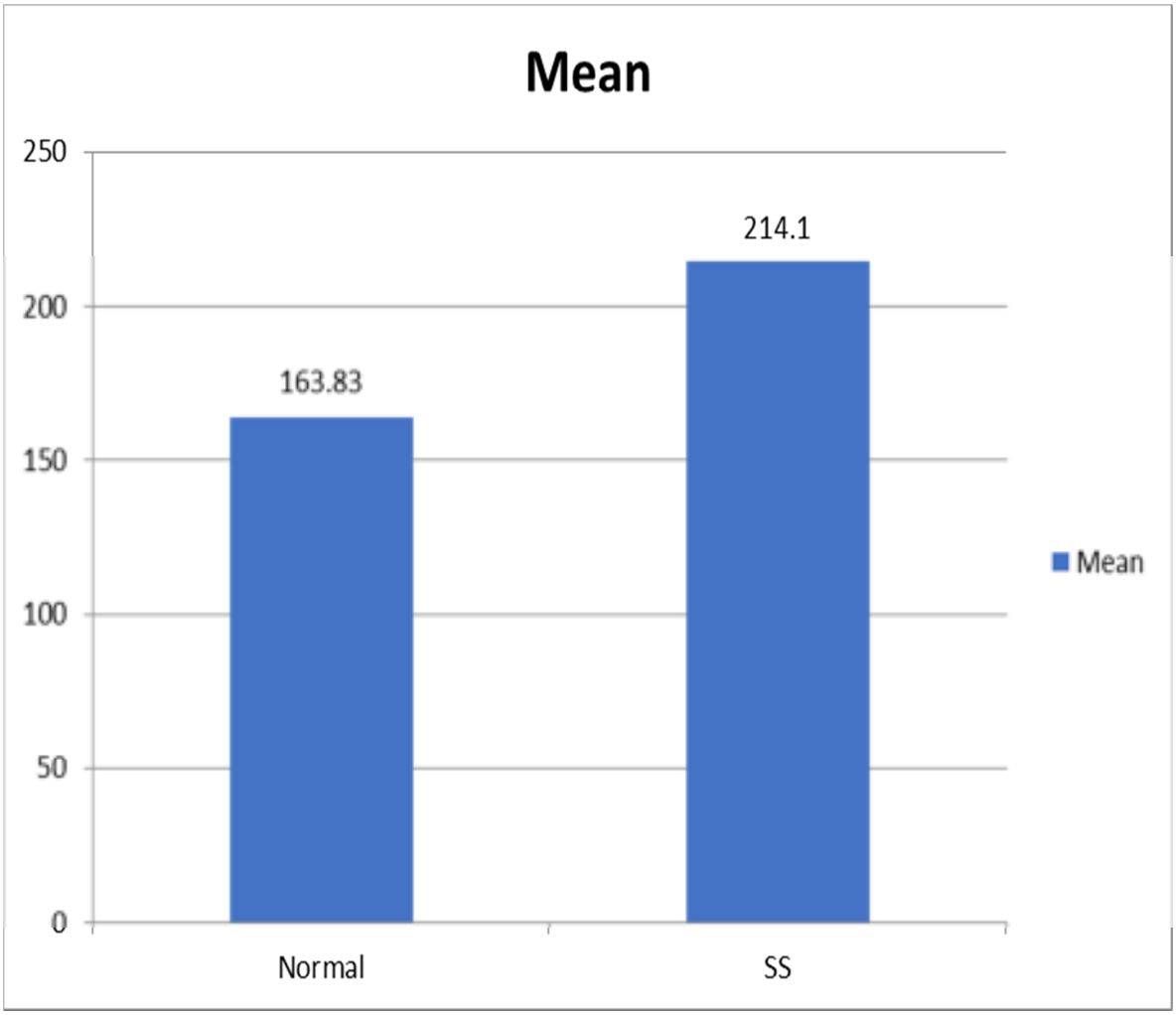
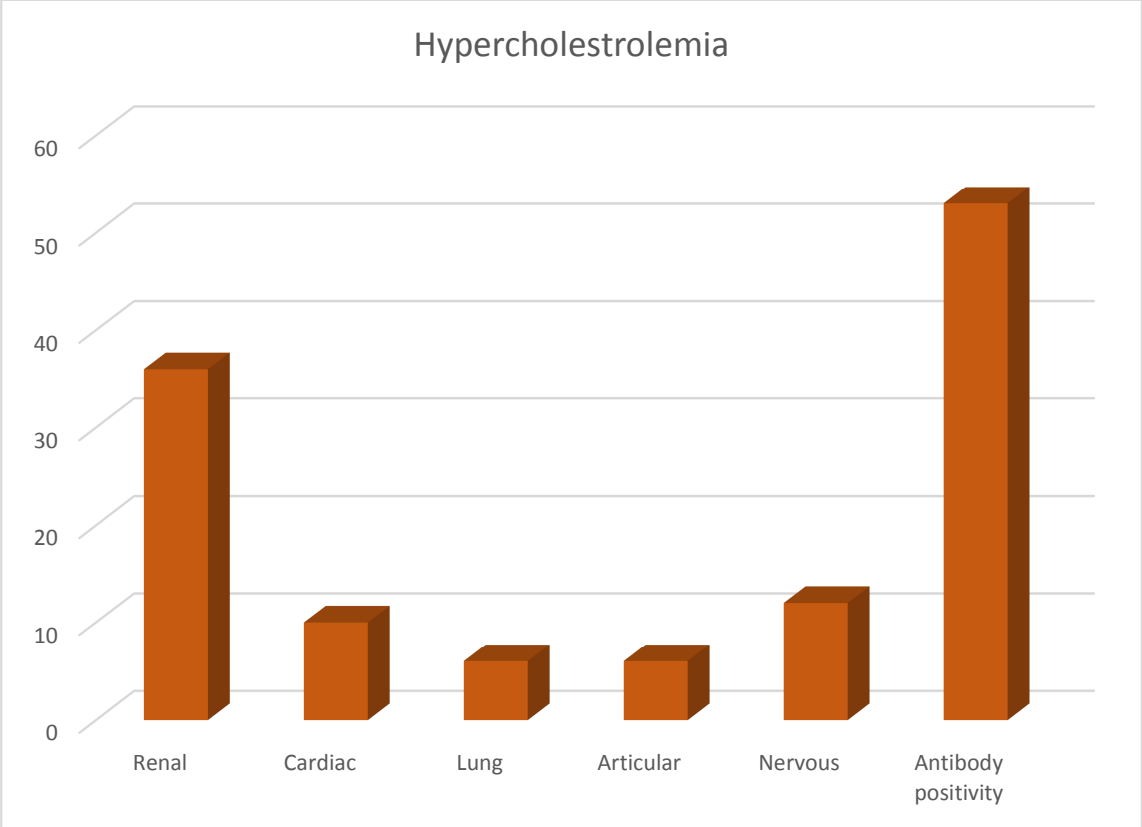


CHART 3b Showing prevalence of hypercholesterolemia with other systemic manifestations



Conclusion:

The serum cholesterol values in patients with SS are higher than the that of normal individuals of same age group. The difference is true and significant.

(p value 0.000)

Table No 6a shows the level of *TGL* among the Control and SS Patient			
TGL			
Normality	Mean	N	Std. Deviation
Normal	105.9333	30	41.44288
SS	163.5000	30	65.17655
Total	134.7167	60	61.43871

Table No 6b Shows the Summary of *ANOVA* for the scores of control and SS patients in *TGL*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
TGL * Normality	Between Groups		49708.817	1	49708.817	16.665	.000
	Within Groups		172999.36	58	2982.748		
	Total		222708.18	59			

CHART 4a showing the prevalence of hypertriglyceridemia

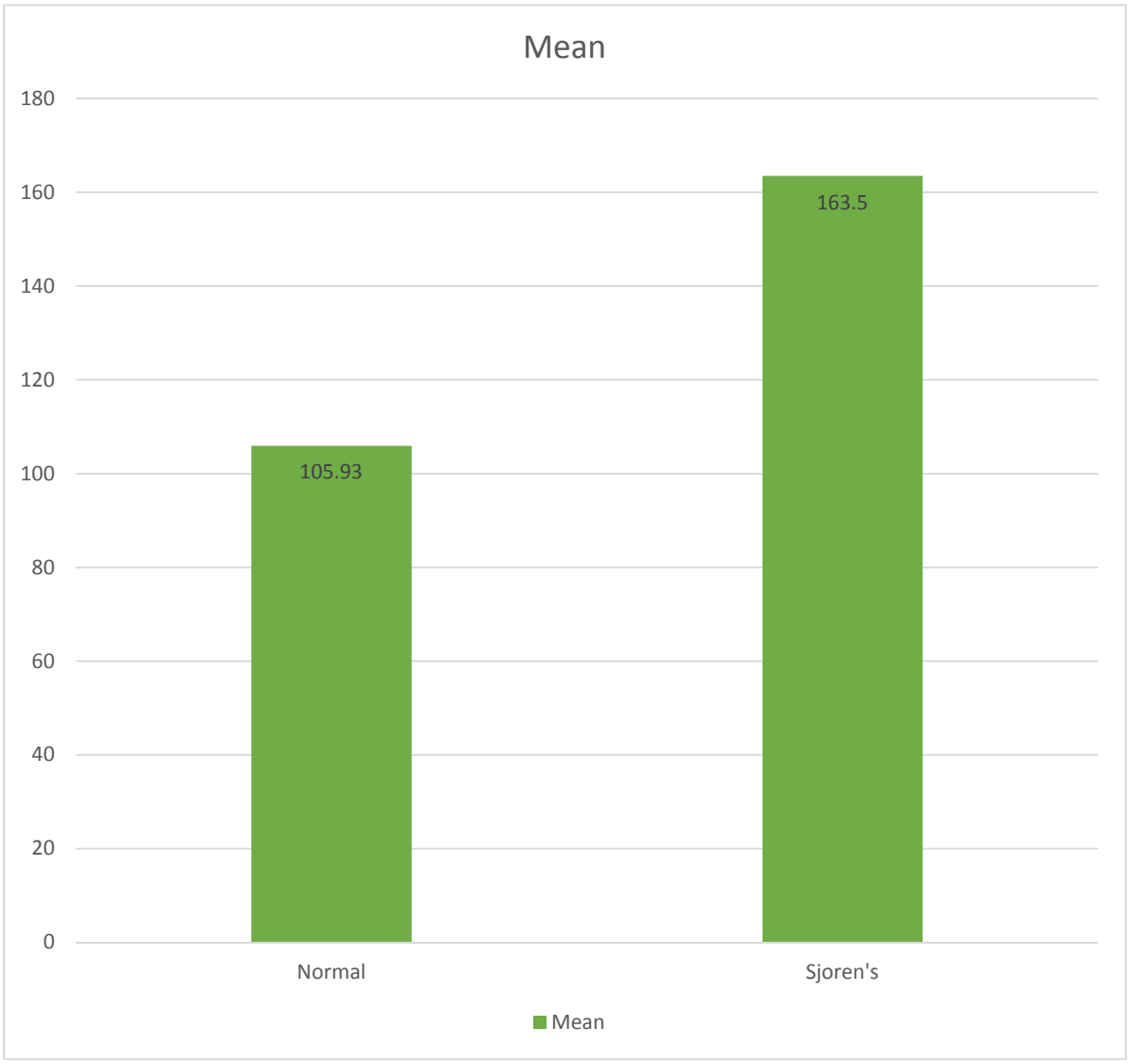
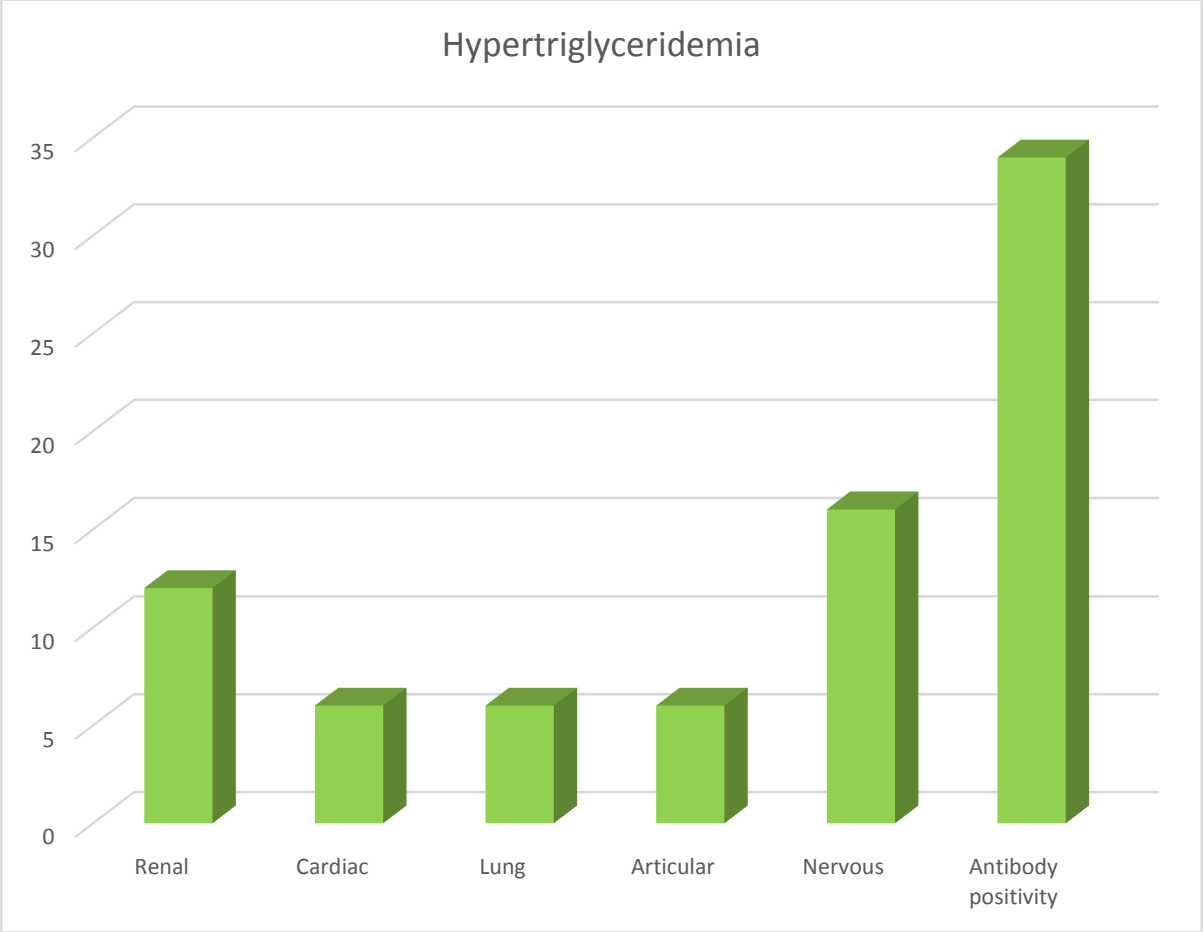


CHART 4b showing the prevalence of hypertriglyceridemia with other systemic manifestations



Conclusion:

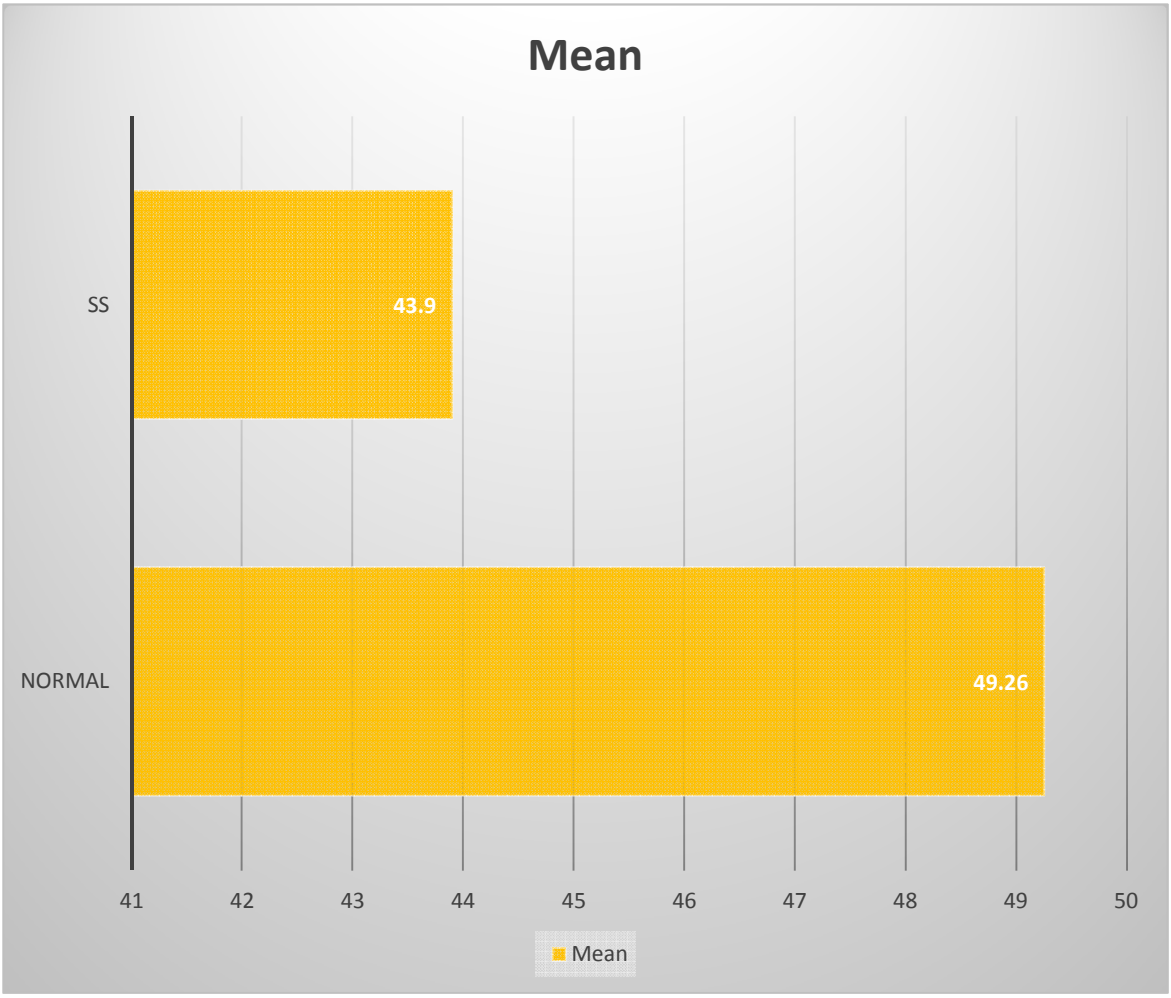
The patients with SS have higher TGL values than the age and sex matched controls. The difference is significant and true. (p value 0.000)

Table No 7a shows the level of *HDL* among the control and SS Patients			
HDL			
Normality	Mean	N	Std. Deviation
Normal	49.2667	30	8.14918
SS	43.9000	30	7.25568
Total	46.5833	60	8.11421

Table No 7b Shows the Summary of *ANOVA* for the scores of control and SS patients in *HDL*

ANOVA Table							
			Sum of Squares	Df	Mean Square	F	Sig.
HDL * Normality	Between Groups		432.017	1	432.017	7.257	.009
	Within Groups		3452.567	58	59.527		
	Total		3884.583	59			

CHART 5 showing Sr. HDL distribution of the control group and SS patients



Conclusion*:*

The HDL value among control group is higher than the that in SS patients. The difference is true and significant. (p value 0.009)

Table No 8a shows the level of *LDL* among the control and SS Patient

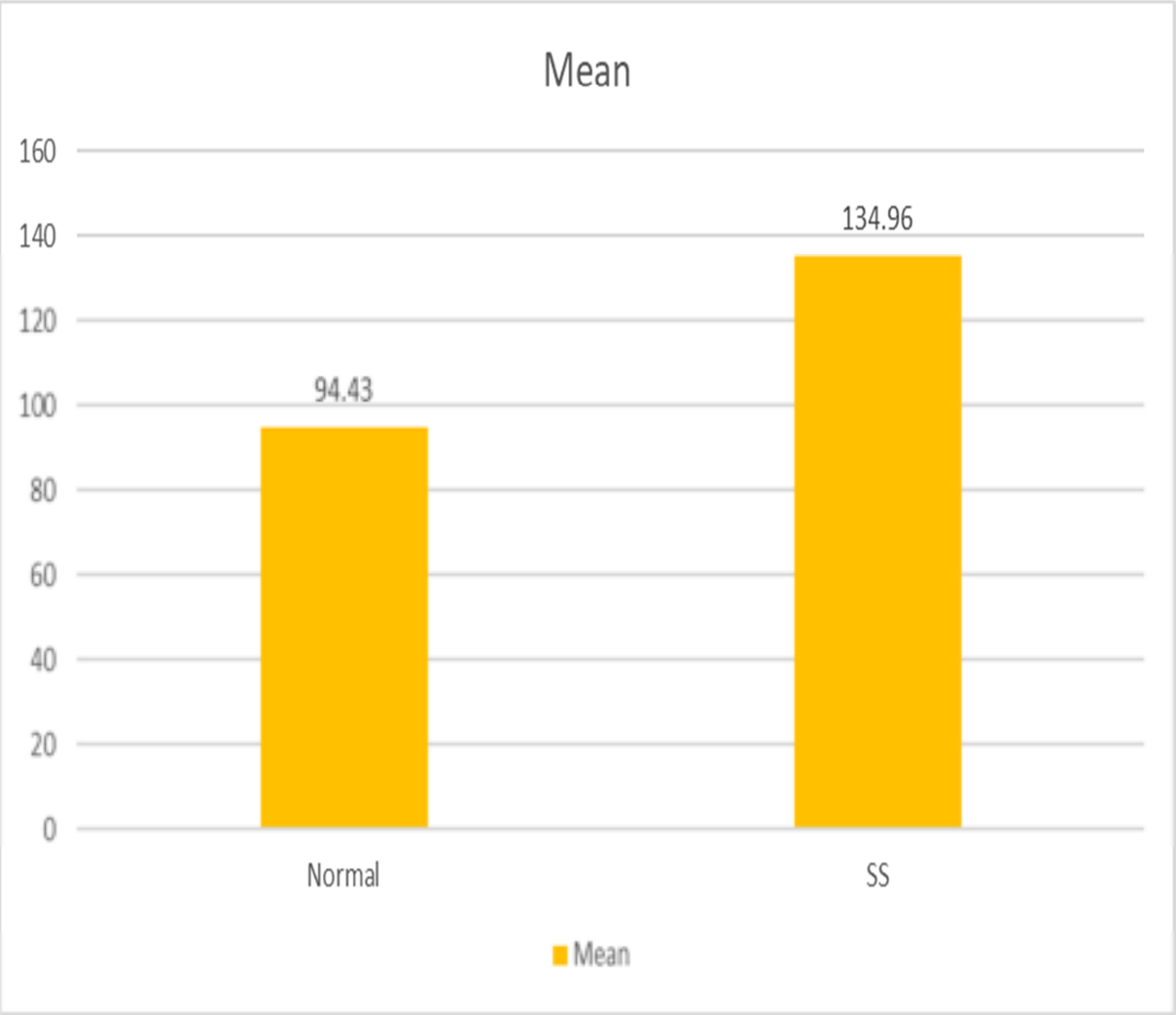
LDL			
Normality	Mean	N	Std. Deviation
Normal	94.4333	30	37.17589
SS patients	134.9667	30	50.53472
Total	114.7000	60	48.49997

Table No 8b Shows the Summary of *ANOVA* for the scores of control and SS patients in *LDL*

ANOVA Table

			Sum of Squares	Df	Mean Square	F	Sig.
LDL * Normality	Between Groups		24644.26	1	24644.2	12.523	.001
	Within Groups		114138.3	58	1967.90		
	Total		138782.6	59			

CHART 6 showing distribution of Sr. LDL values among control group and SS patients



Conclusion:

The LDL values in patients with SS are higher than that of the control group. The difference is true and significant. (p value 0.001

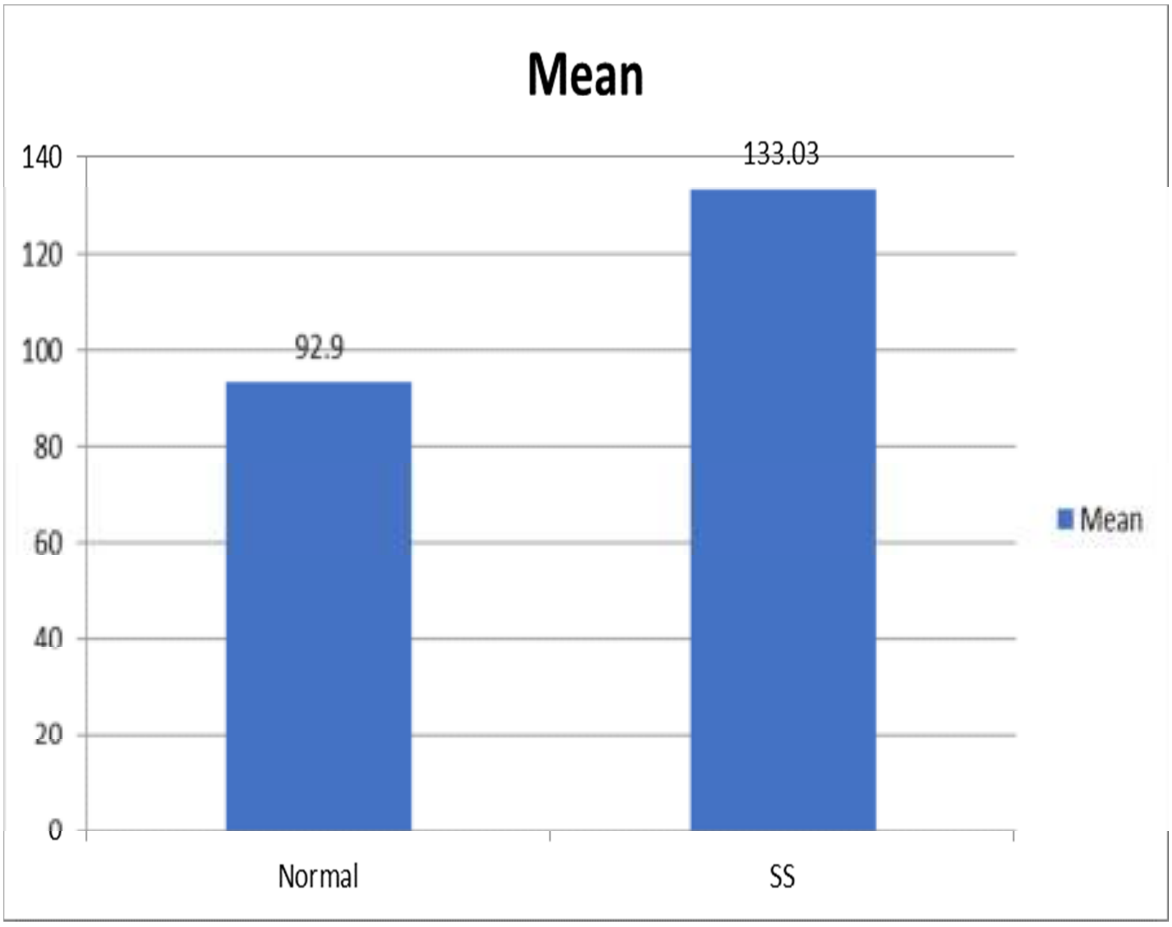
Table No 9a shows the level of *FBS* among the control and SS Patients

Report			
FBS			
Normality	Mean	N	Std. Deviation
Normal	92.9000	30	17.85642
SS	133.0333	30	45.88402
Total	112.9667	60	40.01312

Table No 9b Shows the Summary of *ANOVA* for the scores of control and SS patients in *FBS*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
FBS * Normality	Between Groups		24160.267	1	24160.267	19.933	.000
	Within Groups		70301.667	58	1212.098		
	Total		94461.933	59			

CHART 7 showing distribution of FBS among control group and SS patient



Conclusion:

The FBS values in patients with SS are higher than that of the control group. The difference is true and significant. (p value 0.000)

Table No 10a shows the level of *HBA1C* among the control and SS Patients

Report

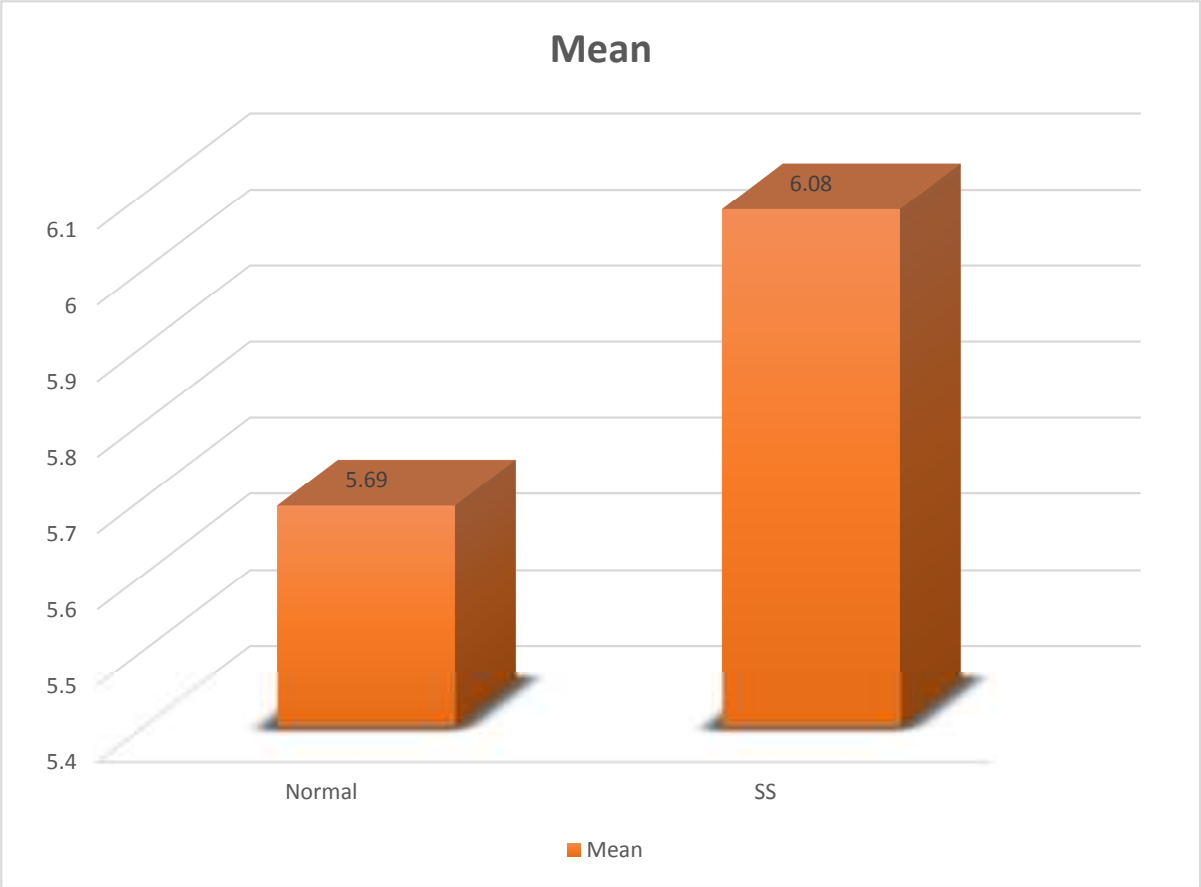
Hba1C			
Normality	Mean	N	Std. Deviation
Normal	5.6967	30	.48458
SS	6.0833	30	1.04785
Total	5.8900	60	.83254

Table No 10b Shows the Summary of *ANOVA* for the scores of control and SS patients in *HBA1C*

ANOVA Table

			Sum of Squares	df	Mean Square	F	Sig.
Hba1C * Normality	Between Groups		2.243	1	2.243	3.365	.072
	Within Groups		38.651	58	.666		
	Total		40.894	59			

CHART 8 showing distribution of HbA1c levels in control group and SS



Conclusion:

Hba1C values of the control group and SS patients do not differ. From the above two variables namely FBS values and HbA1c values, the prevalence of Diabetes Mellitus among the control group and SS patients is estimated. This is done considering either one of the two being positive for the diagnosis of Diabetes Mellitus.

CHART 8b showing the distribution of Diabetes Mellitus in SS patients along with other systemic manifestations

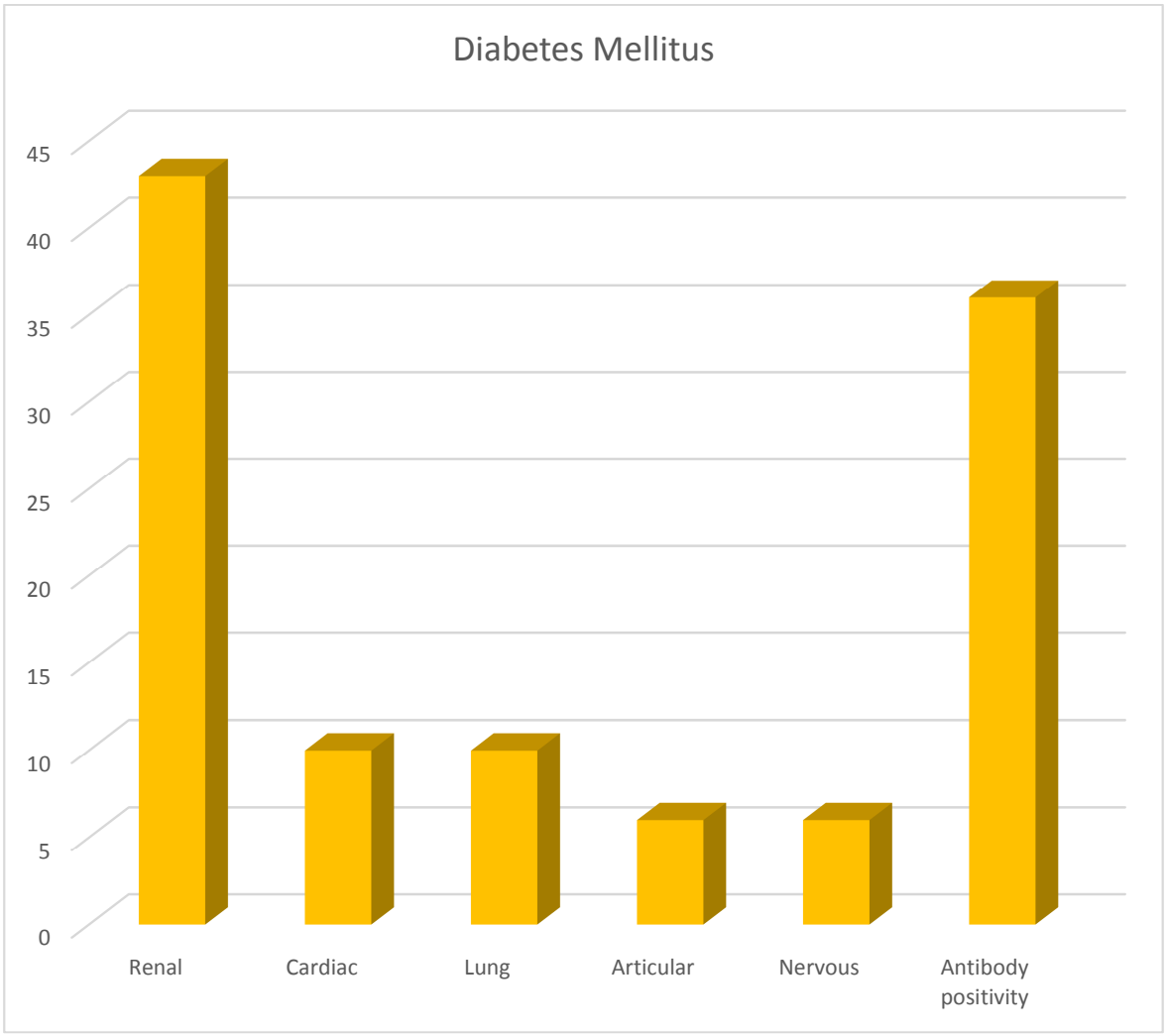


Table No 11a shows the level of *Creatinine* among the control and SS Patients

Report

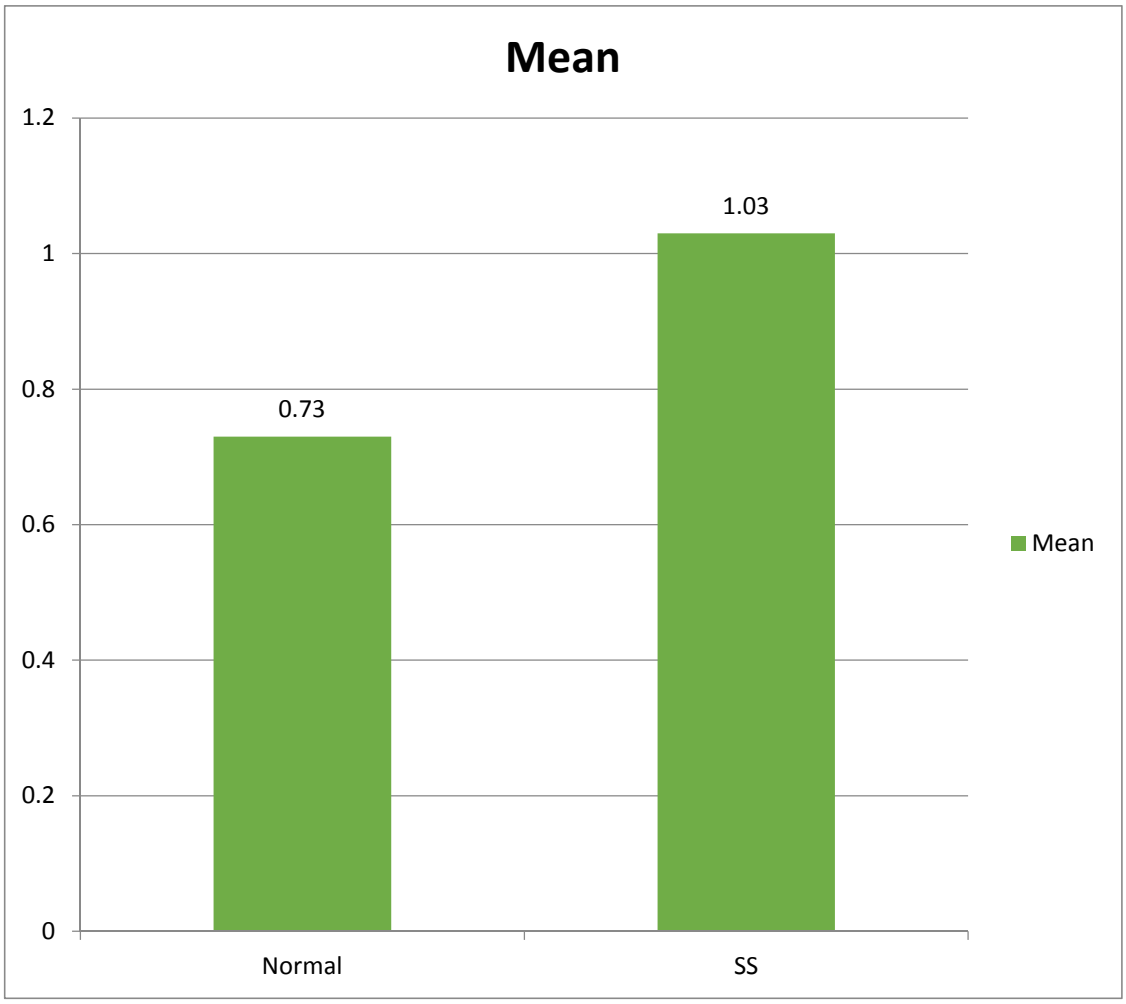
Creatinine			
Normality	Mean	N	Std. Deviation
Normal	.7300	30	.22461
SS	1.0367	30	.41728
Total	.8833	60	.36646

Table No 11b shows the Summary of *ANOVA* for the scores of control and SS patients in *Creatinine*

ANOVA Table

			Sum of Squares	df	Mean Square	F	Sig.
Creatinine * Normality	Between Groups		1.411	1	1.411	12.56	.001
	Within Groups		6.513	58	.112		
	Total		7.923	59			

CHART 9 showing distribution of Sr. Creatinine among control group and SS patients



Conclusion:

The serum CREATININE values in SS patients are higher than that of the control group. The difference is true and significant. (p value 0.001)

Table No 12a shows the level of eGFR among the control and SS Patients

Report

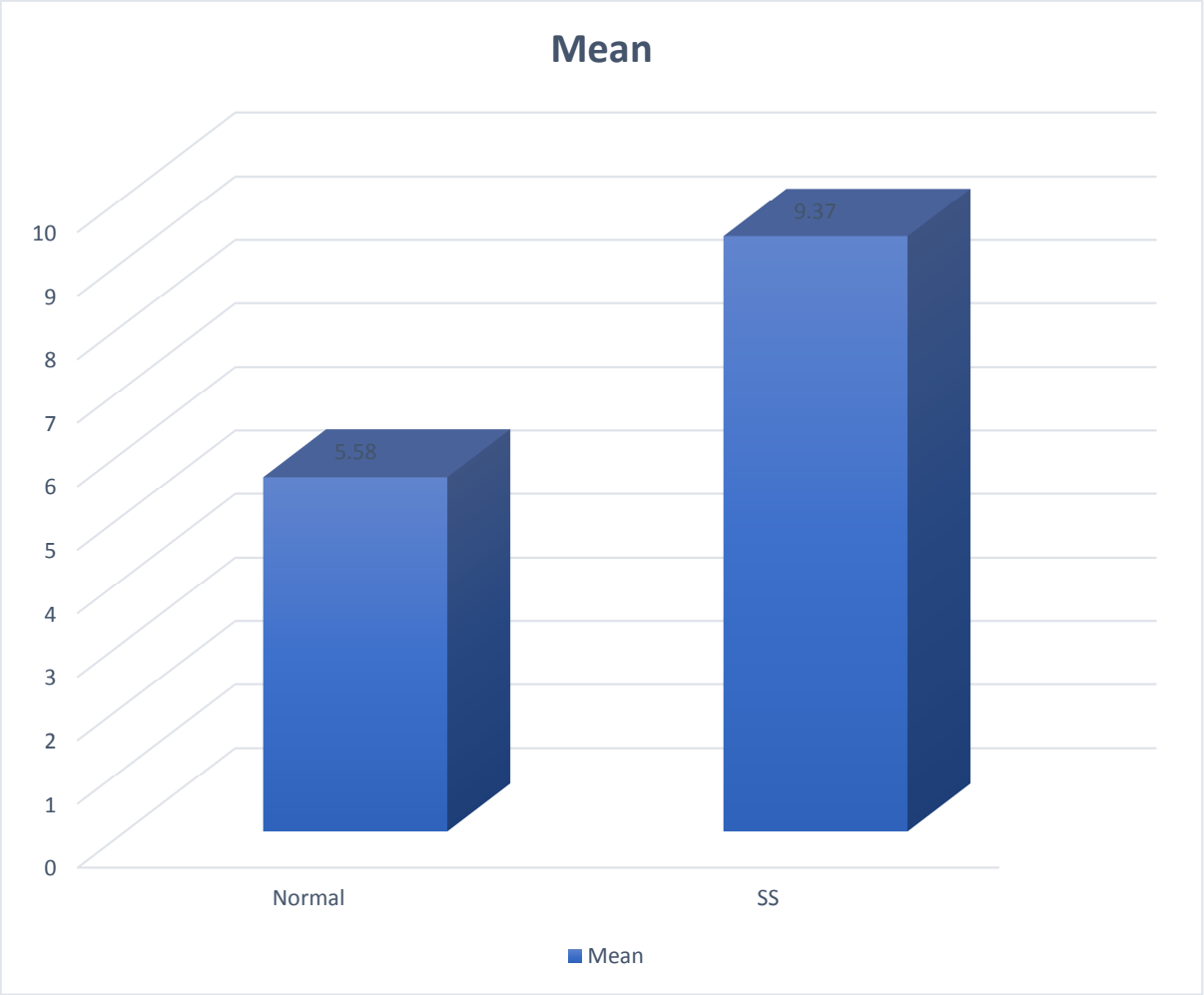
Egfr			
Normality	Mean	N	Std. Deviation
Normal	104.8733	30	28.21532
SS patients	77.8300	30	34.91357
Total	91.3517	60	34.29852

Table No 12b shows the Summary of *ANOVA* for the scores of control and SS patients in eGFR

ANOVA Table

			Sum of Squares	df	Mean Square	F	Sig.
Egfr * Normality	Between Groups		10970.128	1	10970.128	10.888	.002
	Within Groups		58436.782	58	1007.531		
	Total		69406.910	59			

CHART 10 showing distribution of eGFR among control group and SS patients



Conclusion:

The EGFR values in patients with SS are lower than that compared to age and sex matched individuals proving predisposition for renal failure. The difference is true and significant. (p value 0.002)

Table No 13a shows the level of *URIC ACID* among the control and SS Patients

Report

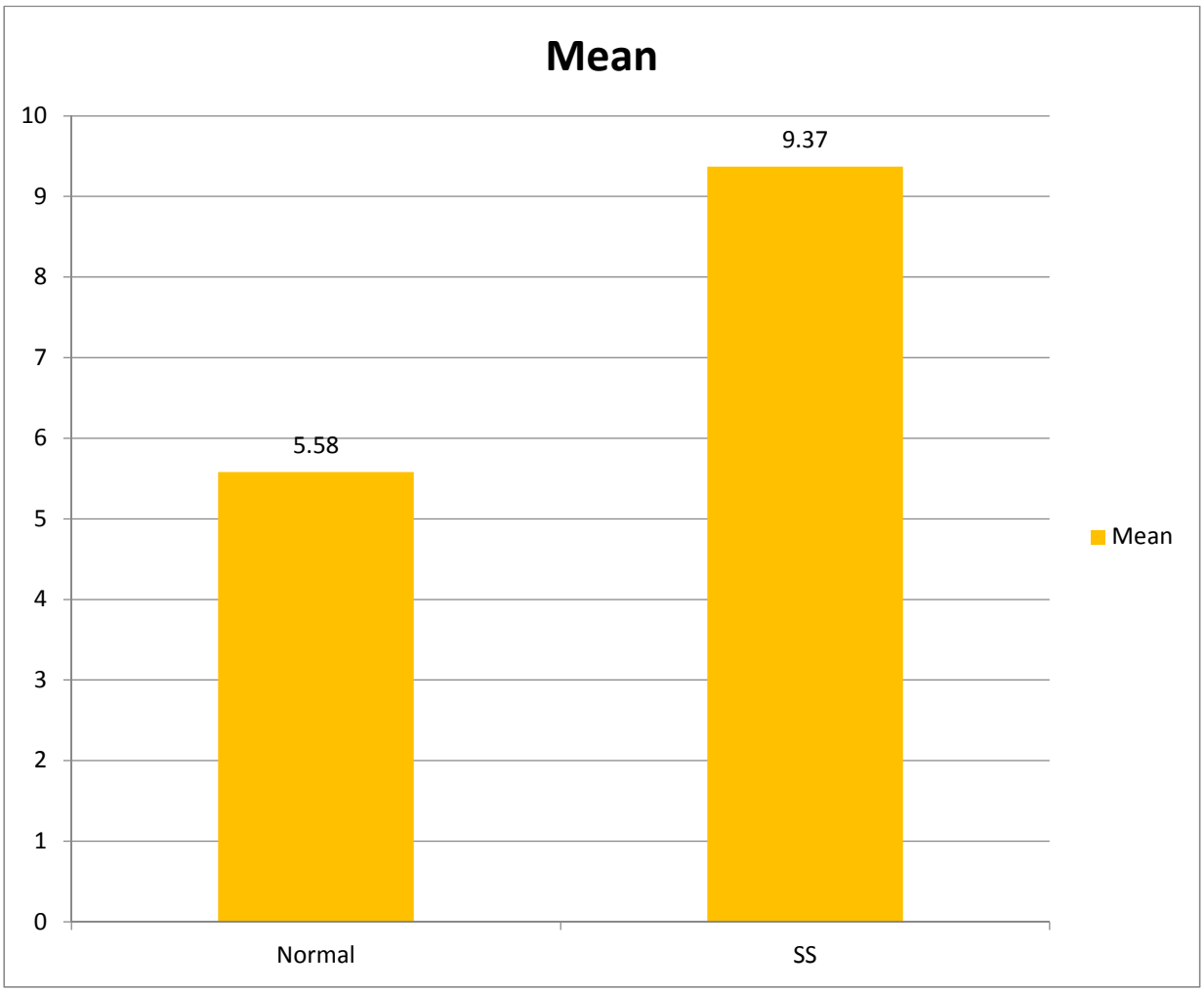
UricAcid			
Normality	Mean	N	Std. Deviation
Normal	5.5867	30	.55754
SS	9.3700	30	3.88544
Total	7.4783	60	3.34847

Table No 13b Shows the Summary of *ANOVA* for the scores of control and SS patients in *URIC ACID*

ANOVA Table

			Sum of Squares	df	Mean Square	F	Sig.
UricAcid * Normality	Between Groups		214.704	1	214.704	27.870	.000
	Within Groups		446.818	58	7.704		
	Total		661.522	59			

CHART 11 showing distribution of Sr. uric acid among control group and SS patients



Conclusion:

The serum URIC ACID values in SS patients are higher than the control group. The difference is true and significant. (p value 0.000)

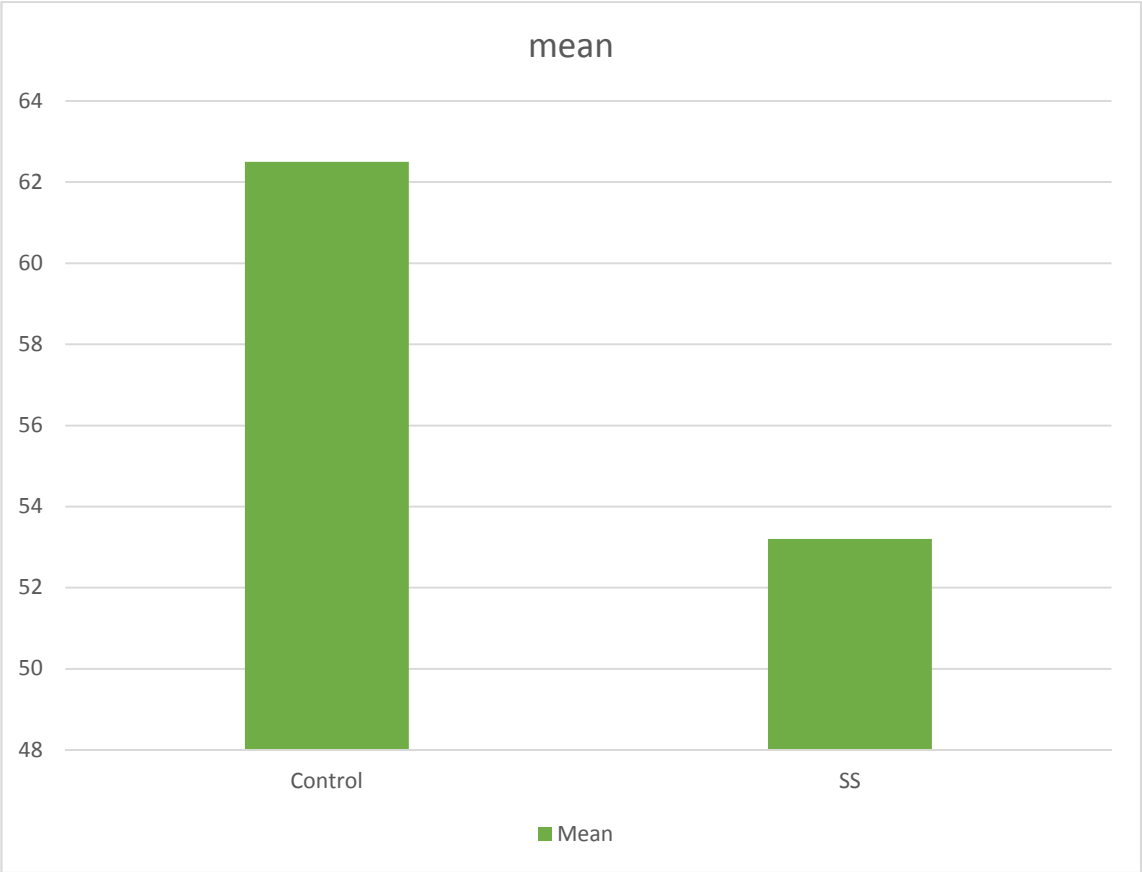
Table No 14a shows the level of *EF* among the control and SS Patients

Report			
EF			
Normality	Mean	N	Std. Deviation
Normal	59.6000	30	4.14895
SS	56.4333	30	7.83750
Total	58.0167	60	6.41896

Table No 14b Shows the Summary of *ANOVA* for the scores of control and SS patients in *EF*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
EF * Normality	Between Groups		150.417	1	150.417	3.825	.055
	Within Groups		2280.567	58	39.320		
	Total		2430.983	59			

CHART 12 showing distribution of EF among control group and SS patients



Conclusion:

The SS patients EF value is lower than the normal patient values. The difference is true and significant. (p value 0.055)

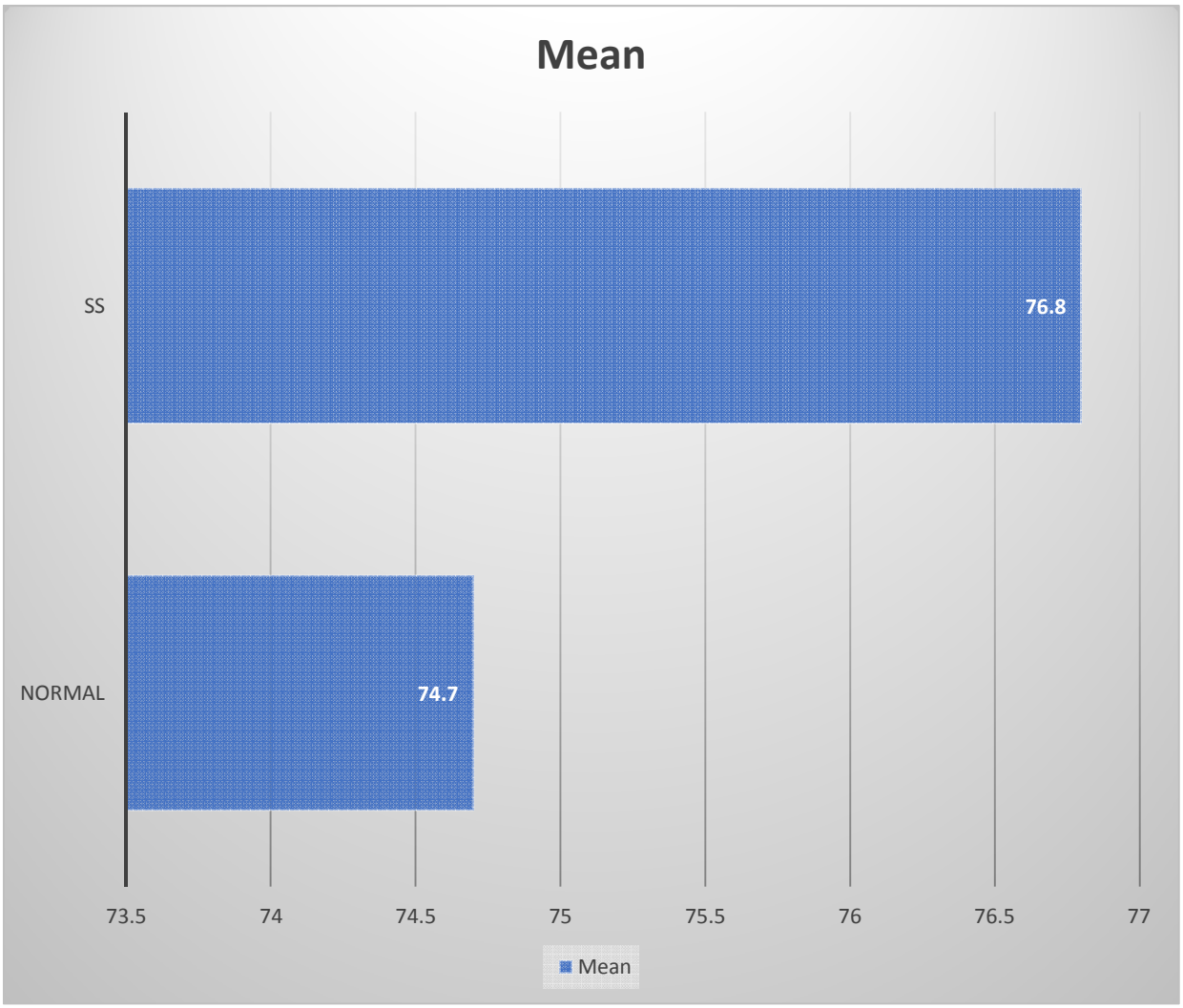
Table No 15a shows the level of *WAIST CIRCUMFERENCE* among the control and SS Patients

Report			
waist			
Normality	Mean	N	Std. Deviation
Normal	74.7000	30	6.71668
SS	76.8000	30	9.24904
Total	75.7500	60	8.08352

Table No 15b Shows the Summary of *ANOVA* for the scores of control and SS patients in *WAIST CIRCUMFERENCE*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
waist * Normality	Between Groups		66.150	1	66.150	1.013	.318
	Within Groups		3789.100	58	65.329		
	Total		3855.250	59			

CHART 13 showing distribution of waist circumference among control and SS patients



Conclusion:

No difference between the control and SS patients in their waist circumference measures.

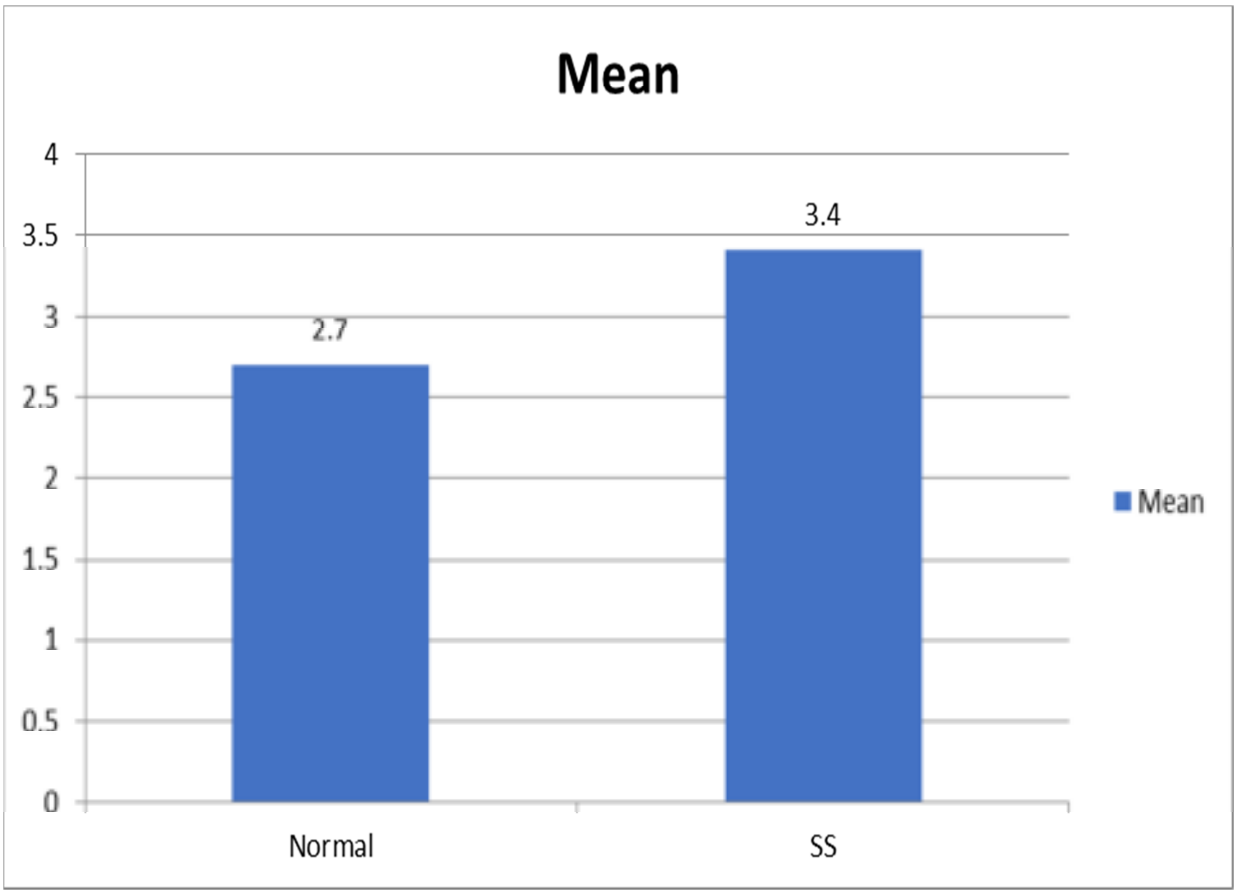
Table No 16a shows the level of *TSH* among the control and SS Patients

Report			
TSH			
Normality	Mean	N	Std. Deviation
Normal	2.7667	30	.67840
SS	3.4767	30	1.54935
Total	3.1217	60	1.23866

Table No 16b Shows the Summary of *ANOVA* for the scores of Normal and Diabetic patients in *TSH*

ANOVA Table							
			Sum of Squares	Df	Mean Square	F	Sig.
TSH * Normality	Between Groups		7.562	1	7.562	5.286	.025
	Within Groups		82.960	58	1.430		
	Total		90.522	59			

CHART 14 showing distribution of TSH among control group and SS patients



Conclusion:

The SS patients TSH values are higher than the control values. The difference is true and significant. (p value 0.025)

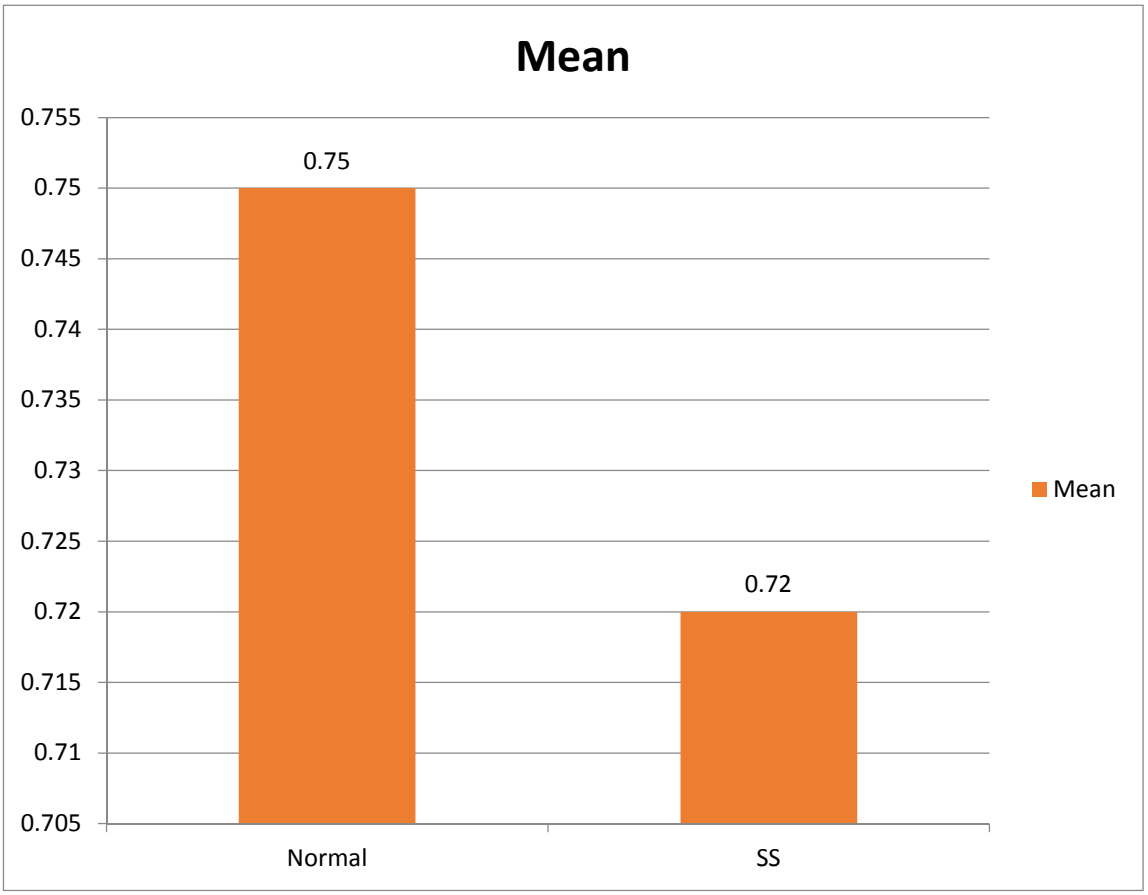
Table No 17a shows the level of *BILIRUBIN* among the control and SS Patients

Report			
Bilirubin			
Normality	Mean	N	Std. Deviation
Normal	.7567	30	.16750
SS	.7233	30	.19420
Total	.7400	60	.18058

Table No 17b Shows the Summary of *ANOVA* for the scores of control and SS patients in *BILIRUBIN*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
Bilirubin * Normality	Between Groups		.017	1	.017	.507	.479
	Within Groups		1.907	58	.033		
	Total		1.924	59			

CHART 15 showing distribution of Sr. bilirubin among control group and SS patients



Conclusion:

No difference has been noted between the control and SS patients in their BILIRUBIN value.

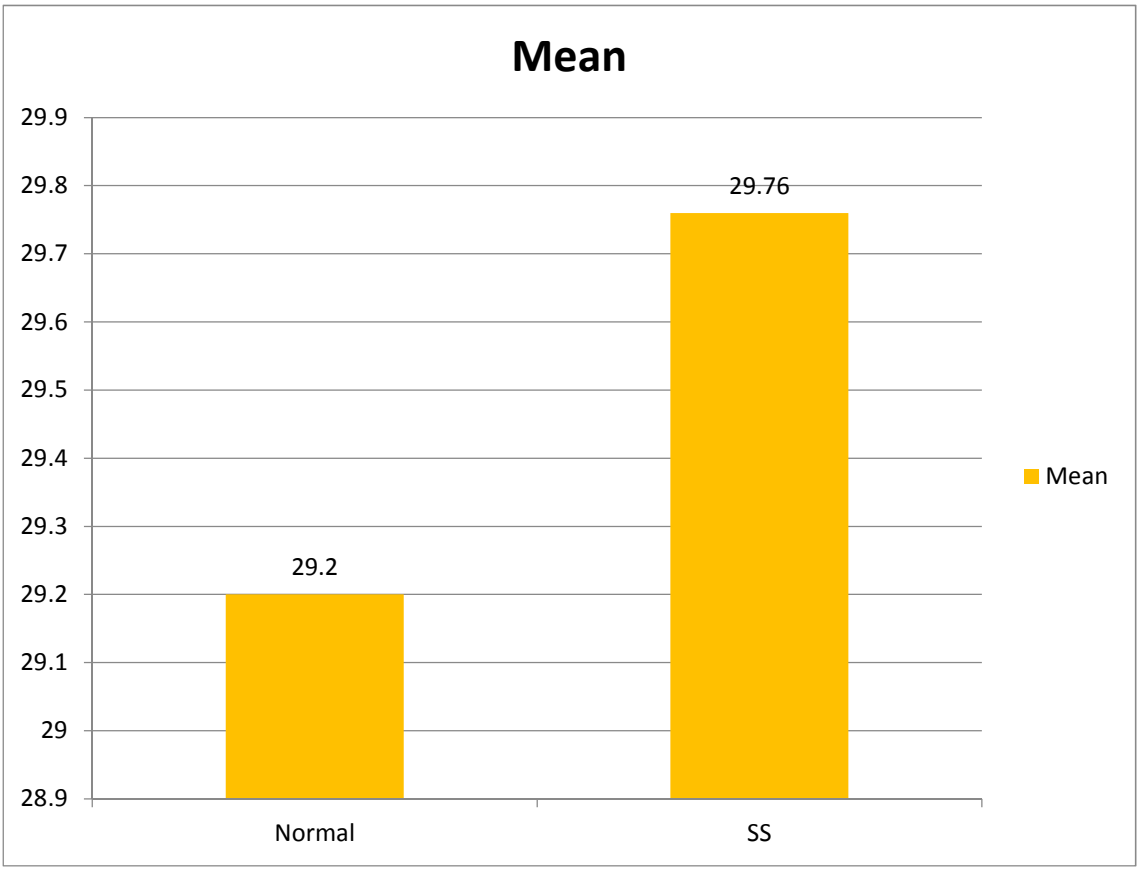
Table No 18a shows the level of *ALT* among the control and SS Patients

Report			
ALT			
Normality	Mean	N	Std. Deviation
Normal	29.2000	30	5.66538
SS	29.7667	30	8.70863
Total	29.4833	60	7.28940

Table No 18b Shows the Summary of *ANOVA* for the scores of control and SS patients in *ALT*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
ALT * Normality	Between Groups		4.817	1	4.817	.089	.766
	Within Groups		3130.167	58	53.968		
	Total		3134.983	59			

CHART 16 showing distribution of Sr. ALT among control group and SS patients



Conclusion:

No difference between the control and SS patients in their ALT value.

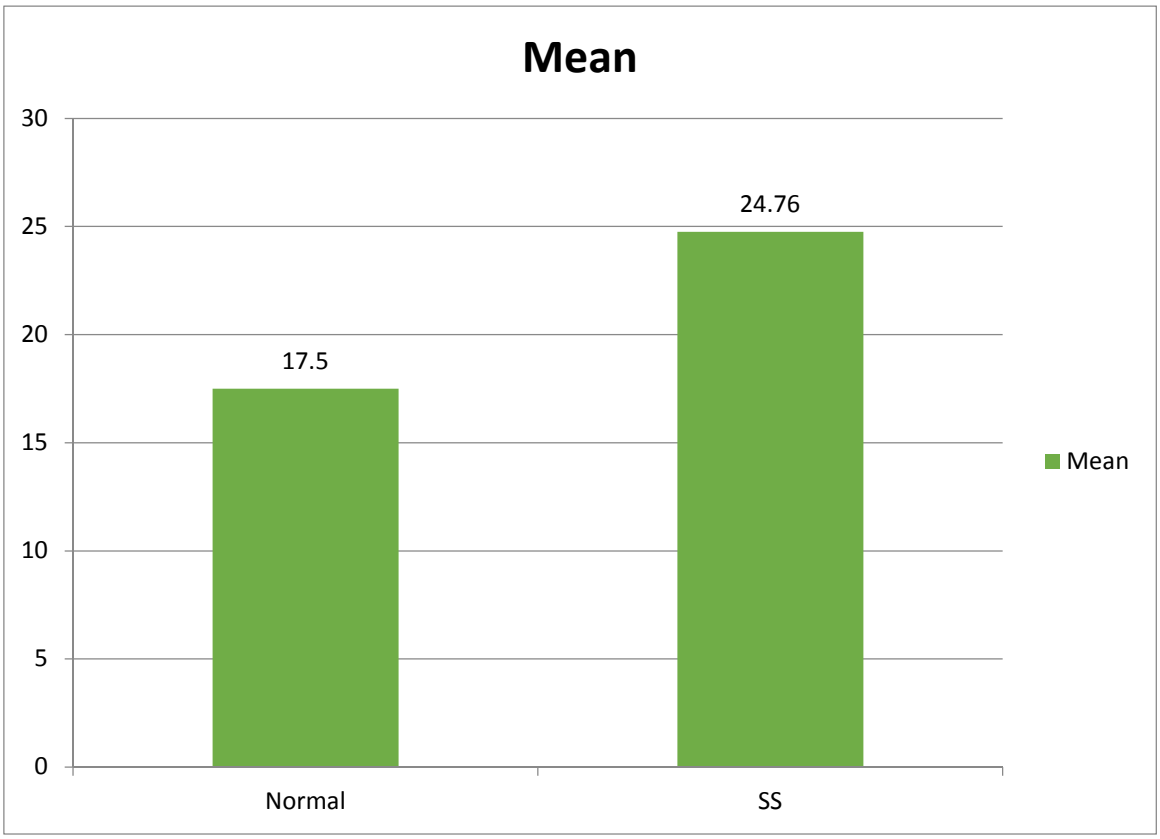
Table No 19a shows the level of *ESR* among the control and SS Patients

Report			
ESR			
Normality	Mean	N	Std. Deviation
Normal	17.5000	30	5.41231
SS patients	24.7667	30	13.64496
Total	21.1333	60	10.92419

Table No 19b Shows the Summary of *ANOVA* for the scores of control and SS patients in *ESR*

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
ESR * Normality	Between Groups		792.067	1	792.067	7.352	.009
	Within Groups		6248.867	58	107.739		
	Total		7040.933	59			

CHART 17 showing distribution of ESR among control group and SS patients



Conclusion:

The SS patients ESR values are higher than that of the control group value. The difference is true and significant. (p value 0.009)

DISCUSSION

In this study, we tried to establish a positive correlation between the high prevalence of hyperlipidemia, hyperglycemia and hyperuricemia in patients with SS when compared to the age and sex matched control population. This study was conducted in a span of one year duration at Coimbatore Medical College Hospital. It was carried out as a cross sectional study. According to this study, a close association was established between the patients with SS and the above mentioned metabolic alterations.

Hypercholesterolemia was found to be the most common metabolic abnormality among the SS patients. In this study of 30 patients of SS, the prevalence of hypercholesterolemia was noted in 17 patients with SS accounting to about 56% of the study population. Among these patients with elevated sr. cholesterol (n=17) , renal impairment in the form of reduced eGFR was noted in 10 patients (58%). In our study, out of these 17 patients with hypercholesterolemia only one patient had a significant reduction in the Ejection Fraction. All these 17 patients with hypercholesterolemia were proved to be positive for Anti- Ro and Anti- La antibodies. Interstitial lung disease was found in only two patients among those with hypercholesterolemia.

The second common metabolic abnormality noted was hypertriglyceridemia. Out of the 17 patients with hypercholesterolemia, around 16 had elevated triglyceride level. This in turn was found to contribute to the reduction of eGFR in patients with SS.

Diabetes mellitus was the next commonly prevalent metabolic alteration noted in 16 patients of the study population (53%). Out of these 16 patients, only one was below 30 years of age, 6 patients were between 30 to 40 years and 9 patients above 40 years. This showed a positive correlation between increase in the prevalence of diabetes in Sjogren's syndrome patients with increase in age. Of these 16 patients with diabetes 10 had a significant reduction in eGFR which accounts for around 62%. hence the risk of development of renal failure in Sjogren's syndrome patients is increased manifold by coincident diabetes mellites when compared to other metabolic variables.

Hyperuricemia was noted in 13 patients with SS (n=30) which accounts to about 40%. The eGFR was found to be reduced in about 12 patients among the 13 (92%). Among these patients 0ne patient was in stage IV (eGFR -27) . three patients were in stage IIIb. So a higher level of sr. uric acid was found in Sjogren's patients with renal failure.

Serum HDL level was found to be significantly low in patients with SS which further contributed to the ill effects. Schirmer's test was invariably positive in patients with SS.

Anti nuclear antibodies and Rheumatoid factor were negative in all the 30 patients with Sjogren's syndrome thus ruling out the possibility of secondary SS leading on to these alterations of metabolic parameters. The serum complement levels were not reduced in the study population. Those

patients with reduced eGFR also showed a normal serum levels of complement thus excluding the possibility of mesangioproliferative pattern of glomerular injury which is more commonly seen in patient with lupus nephritis.

The thyroid peroxidase levels are positive only in 5 patients with SS in our study. Liver function test done in our study population did not show any significant alterations.

Extraglandular manifestions like joint involvement, neuropathies did not show any positive correlation in our study. Only 2 patients among the control group showed erosion in the joints as indicated by xray studies. 6 patients with SS showed abnormal nerve conduction studies. Among these 6 patients, sensory pattern was predominant than motor or mixed patters in the nerve conduction study.

SUMMARY

Sjogren's syndrome is a systemic, chronic, autoimmune, inflammatory disorder characterized by lymphocyte infiltration into the exocrine organ. It is thought to be due to ongoing iteration between innate and acquired immune systems. There is presence of activated salivary gland epithelial cells expressing MHC Class II molecules. Some evidence indicates that the true association of Sjogren's syndrome may be with HLA-DQA1.the possible triggers factors may be a viral etiology mainly Ebstein-Barr virus, HTLV-1, HHV-6, HIV, Hepatitis c virus and Cytomegalovirus. The female to male ratio is 9:1. Periepithelial infiltrative process include interstitial nephritis, liver involvement, liver involvement, bronchiolitis.

In our study we compared various metabolic parameters in patients with Sjogren's syndrome with that of the age and sex matched control group. A higher prevalence of metabolic alterations mainly that of hypercholesterolemia , hyperuricemia and diabetes were noted in these patients.

The effect of these metabolic alterations was also studied. A greater percentage of these patients were found to have a reduction in the glomerular filtration rate.

Hypercholesterolemia begin the most common among the patients with Sjogren's syndrome. There are experimental studies supporting the possibility of lipid abnormality in the etiopathogenesis of primary SS. There were studies supporting the evidence of parotid enlargement being more prevalent in patients with hypertriglyceridemia.

The prevalence of diabetes mellites was also established in these patients. There are studies suggesting that these metabolic alterations might worsen the inflammatory process in primary SS patients. This in tun may contribute to the involvement of the vasculature.

In SS patients with altered liver profile in the form of elevated serum bilirubin or liver enzymes like ALT, there was a higher prevalence of hypertriglyceridemia and diabetes mellitus.

In regard to patients with hyperuricemia, patients with high frequency of renal failure had a higher incidence of increased uric acid levels.

From our study the close association between serum metabolic alterations and Sjogren's syndrome has been clearly established. Hence the classification, prognosis and therapeutic management of patients with primary SS has been debated. Thus, the real etiology for the development of metabolic alterations in SS could be either an immune mediated phenomenon or any metabolic disease that might mimic SS.

According to our study, the difference between SS alone and those with metabolic derangements could not be well established by the existing classification criteria. Thus, a newer classification named primary SS with differentiated etiopathogenetic mechanism has been proposed.

Though there is a relation between atherosclerosis and patients with primary SS, the overall cardiovascular mortality was not found to be quite significant in these patients.

A few therapeutic agents like thiazolidinediones, metformin, antioxidants and statins might have a potential role for treatment of primary SS in near future. statins have been proved to have a pleotrophic effort apart from their lipid lowering effect. Atorvastatin has a special role with anti-inflammatory and immunomodulatory action in primary SS. Hence it has been proved to have a promising role in the treatment of systemic autoimmune diseases with coexisting metabolic alteration. There have been previous studies suggesting a superior role of immunomodulators (antimalarials) when compared with corticosteroids in the treatment of metabolic alterations in Sjogren s syndrome. Hence it has been suggested to limit the use of corticosteroids in treatment of SS with extraglandular manifestations alone with the least possible dose. When the use of corticosteroid therapy is indicated for a prolonged duration, the supplementation with biological agents or immunomodulators has been advised.

LIMITATIONS

Being a cross sectional study, the effect of treatment underwent by these patients could not be assessed. Another limitation of this study is that the outcome of patients who received immune modulators (antimalarials) and biological agents could not be studied. Moreover, the cause for the reduction in the glomerular filtration rate, whether it was an immune mediated process or a metabolic alteration leading on to a reduction in the eGFR couldn't be established properly. Being an invasive procedure renal biopsy was not attempted in these patients.

CONCLUSION

A study on the metabolic alterations in patients with primary Sjogren's Syndrome was conducted in Coimbatore Medical College Hospital during the period of May 2017 to April 2018. The various metabolic parameters – Serum cholesterol, Serum triglycerides, Serum LDL, blood glucose levels and Serum uric acid levels were analysed.

- The high prevalence of the metabolic alterations in patients with primary SS has been established.
- The need for earlier screening and treatment of these metabolic derangements should be considered.
- The rationale behind the use of immunomodulators and biological agents in treatment of the subgroup of SS patients with metabolic alterations when compared with corticosteroids has been proved.

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ANNEXURE I

PROFORMA

Name : Age : Sex : Address :

Height : Weight : Waist Circumference :

Sr. Creatinine : Sr. Uric Acid :

Sr. Cholesterol : Sr. Triglycerides :

Sr. HDL : Sr. LDL :

FBS : HbA1C :

Echocardiography : HRCT :

Schrimer's test : ESR :

NCS : Xray Joints :

Sr. Bilirubin : ALT :

Anti Ro : Anti La :

ANA : RF :

TSH : Anti TPO :

C3 levels : C4 levels :

ANNEXURE II

MASTER CHART- SS PATIENTS

Name	AGE	SR.CH	SR. TGL	SR.HDL	SR.LDL	FBS	HbA1C	SR.CR	eGFR	SR.UA	EF	HRCT	ST	WC	ANTI Ro	ANTI La	ANA	RF	TSH	TPO	C3	C4	SR.BILIRUBIN	ALT	ESR	NCS	XRAY JOINTS
Maragatham	32	240	205	28	171	105	5.2	0.7	103.1	9.2	65	normal	+	82	+	+	-	-	3.5	-	normal	normal	0.9	35	45	normal	normal
Annaporani	38	148	121	42	82	94	5	0.8	85.3	6.1	60	normal	+	75	+	+	-	-	2.9	-	normal	normal	0.7	26	8	normal	normal
Murugalakshmi	44	132	58	53	68	149	7.2	2.1	27.2	14.6	55	normal	+	94	+	+	-	-	4.3	-	normal	normal	0.6	28	10	normal	normal
Baby	24	256	192	32	186	81	5.1	0.6	130.5	5.9	62	normal	+	68	+	+	-	-	2.6	-	normal	normal	0.7	25	13	normal	normal
Nalini	38	268	234	36	186	169	7	1.6	38.3	13.9	54	ILD +	-	72	+	+	-	-	2.3	-	normal	normal	0.8	42	65	normal	normal
Karthika	21	142	88	48	76	105	5.4	0.7	112.3	5.6	65	normal	+	74	-	-	-	-	2.8	-	normal	normal	0.6	41	12	normal	normal
Sampoornam	45	256	170	40	182	102	5.5	1	63.7	6.2	50	normal	+	85	+	+	-	-	2.8	-	normal	normal	0.6	25	20	normal	normal
Mary	35	185	105	35	50	106	5.2	0.5	149.2	10	60	normal	+	75	+	+	-	-	6.5	+	normal	normal	0.7	20	15	normal	normal
Nirmala	37	270	100	50	200	154	7.5	1.2	53.7	6	50	normal	+	80	+	+	-	-	2.4	-	normal	normal	1.2	40	15	sensory	normal
Rosline	36	220	180	40	144	170	7.8	1.1	59.7	7	45	normal	+	76	+	+	-	-	2.1	-	normal	normal	0.5	25	20	sensory	normal
Jothi	42	240	200	45	155	220	6.7	1.2	52.4	17.2	55	normal	+	75	+	+	-	-	2.3	-	normal	normal	0.6	45	24	normal	normal
Lakshmi	36	150	100	52	78	240	7.8	1.8	33.8	12.1	52	ILD+	+	68	-	-	-	-	4	+	normal	normal	0.8	25	14	normal	normal
Balaji	32	145	120	42	79	86	5.6	0.9	103.9	7	65	normal	+	72	+	+	-	-	2.3	-	normal	normal	0.6	20	20	normal	normal
Hemalatha	40	250	210	40	168	146	7.1	1.2	52.9	10	50	normal	+	80	+	+	-	-	1.2	-	low	normal	0.5	25	42	noraml	erosion+
Vahini	24	156	120	45	87	136	6.7	0.9	81.8	12	58	normal	-	53	+	+	-	-	7.2	+	normal	normal	0.6	20	15	normal	normal
Jeyageetha	38	260	210	45	173	142	6.7	1.2	53.4	14	52	normal	+	96	+	+	-	-	2.2	-	normal	normal	1.1	25	28	sensory	normal
Chitra	36	280	225	50	185	106	5.4	0.9	75.3	12.2	60	normal	+	80	+	+	-	-	2.5	-	normal	normal	0.8	30	25	normal	normal
Vinothini	38	298	240	48	202	146	6.8	1.4	44.7	15	42	normal	+	76	+	+	-	-	2.8	-	low	normal	0.6	28	18	sensory	erosion+
Maheshwari	42	245	156	41	173	102	5.6	0.9	73	8.3	68	normal	+	68	+	+	-	+	3.6	-	normal	normal	1	28	42	normal	normal
Vidhya	46	165	92	40	107	146	6.5	0.8	82.1	5.2	65	normal	+	65	-	-	-	-	4	-	normal	normal	0.5	12	24	normal	normal

Radhika	42	246	186	52	154	98	4.5	0.7	97.5	12.4	58	normal	+	76	+	+	-	-	2.8	-	normal	normal	0.8	24	52	normal	normal
Devi	40	280	230	56	178	136	6.8	1.2	52.9	8.6	55	ILD+	+	82	+	+	-	-	2.9	-	normal	normal	0.6	26	22	normal	normal
Devika	42	156	89	45	93	230	7.7	1	64.6	15.8	42	normal	+	76	+	+	-	-	5.2	+	normal	normal	0.8	36	28	normal	normal
Mangaiyarkarasi	34	198	150	45	123	78	4.8	0.5	150.1	4.2	65	normal	+	68	+	+	-	-	4.5	-	normal	normal	0.6	28	38	normal	normal
Nirmala	36	168	94	62	91	84	5.2	0.6	120.2	5.3	60	normal	+	72	+	+	-	-	7.3	+	normal	normal	0.7	25	12	normal	normal
Ramathal	49	259	142	41	189	168	6.4	1.5	39.2	6.8	40	normal	+	86	+	+	-	+	3.2	-	normal	normal	0.6	41	24	sensory	normal
Shankar	34	152	238	43	61	102	5.1	0.8	87.3	5.3	65	normal	+	77	+	+	-	-	2.4	-	normal	normal	0.5	34	15	normal	normal
Kanchana	25	136	123	45	67	83	4.9	0.6	129.5	5.8	65	normal	+	81	+	+	-	-	3.5	-	normal	normal	0.6	25	16	normal	normal
Malar	36	228	169	42	153	103	4.5	0.8	86.3	5.6	60	normal	+	74	+	+	-	-	2.3	-	normal	normal	1.1	38	23	normal	normal
Sarala	41	294	358	34	188	204	6.8	1.9	31	13.8	50	normal	+	98	+	+	-	-	5.9	-	normal	normal	1	51	38	sensory	normal

MASTER CHART- CONTROL GROUP

Name	AGE	SR.CH	SR. TGL	SR.HDL	SR.LDL	FBS	HbA1C	SR.CR	eGFR	SR.UA	EF	HRCT	WC	TSH	TPO	SR.BL	ALT	ESR
Selvi	24	130	58	48	71	86	5.3	0.7	109.3	5.1	65	Normal	74	3.6	-	0.7	41	25
Kanaga	37	143	85	51	75	95	5.1	0.9	74.9	5.3	60	Normal	68	2.3	-	0.9	25	20
Amritham	40	104	69	44	46	72	5.3	0.7	98.5	6.1	61	Normal	76	2.4	-	1.1	24	15
Sangavi	42	116	82	43	57	99	5.4	0.8	84.4	6.4	65	Normal	69	2.8	-	0.8	36	21
Marathal	34	107	61	38	57	84	5.6	0.8	87.3	4.9	62	Normal	73	3.2	-	0.7	20	18
Anbumani	25	194	57	48	135	91	5.8	0.6	129.5	5.6	60	Normal	84	3.3	-	0.5	26	14
Karthik	36	126	89	52	56	93	5.4	0.7	100.6	5.7	55	Normal	75	3.2	-	0.8	28	16
Prema	44	298	240	48	202	97	5.8	0.7	96.6	5.4	60	Normal	80	2	-	0.7	38	15
Vanaja	35	135	101	48	67	82	6.1	0.5	149.2	5.6	55	Normal	77	1.3	-	0.9	29	18
Mani	42	148	124	62	61	84	5.7	0.8	86.8	7.8	60	Normal	86	2.5	-	0.8	25	14
Latha	38	168	94	63	90	85	5.1	0.6	118.9	5.6	53	Normal	72	3.4	-	0.9	26	13
Sowmya	32	162	85	51	94	78	6.2	0.5	152	4.9	55	Normal	68	3.6	-	0.7	24	16
Neela	38	158	96	58	81	96	5.8	0.7	99.5	5.3	60	Normal	82	3.5	-	0.6	29	25
Seetha	45	145	78	43	86	143	7.1	1.3	47.1	5.7	65	Normal	72	2.4	-	0.5	38	24
Anjali	36	192	134	58	108	83	5.3	0.7	120.2	5.6	60	Normal	76	2.1	-	0.8	34	21
Prabha	34	179	88	61	121	101	5.9	0.8	87.3	5.4	60	Normal	70	2.6	-	0.7	32	16

Loganathan	40	151	94	47	89	98	5.7	0.6	117.7	5.8	65	Normal	66	2.3	-	0.5	21	15
Valar	36	148	85	50	81	107	6.3	0.8	86.3	5.7	55	Normal	79	2.5	-	0.9	35	14
Chitra	32	253	198	32	181	96	6.1	0.7	103.1	5.6	56	Normal	76	3.2	-	0.8	32	16
Nirmala	21	159	86	59	83	81	5.4	0.5	165.5	5.3	60	Normal	74	3.3	-	0.5	36	10
Sasikala	42	167	102	45	102	156	6.9	0.7	97.5	4.8	65	ILD +	95	4.1	-	0.8	35	36
Palaniyamal	38	191	126	53	113	102	5.1	0.6	118.9	5.7	60	Normal	70	2.1	-	0.6	32	15
Senthil	42	169	134	47	96	87	5.6	0.7	97.5	5.4	58	Normal	73	2.5	-	0.8	30	16
Bakyam	49	136	91	49	69	76	5.8	0.8	81	5.6	62	Normal	68	1.9	-	0.7	24	15
Divya	32	142	89	56	68	79	5.4	0.6	123.1	5.2	65	Normal	66	2.4	-	0.6	20	12
Pushpa	38	155	107	42	92	88	5.7	0.5	146.8	5.1	61	Normal	64	1.8	-	0.7	25	9
Swarnam	36	162	118	47	92	82	5.6	0.6	120.2	5.3	55	Normal	78	2.4	-	0.9	26	15
Baby	24	177	98	62	95	92	5.3	0.7	109.3	5.6	55	Normal	82	3.8	-	1.2	28	16
Poongodi	48	149	113	38	89	75	5.2	1.6	36.6	6.2	50	Normal	76	3.4	-	0.7	25	24
Elango	36	251	196	35	176	99	5.9	0.7	100.6	5.9	65	Normal	72	3.1	-	0.9	32	21

ANNEXURE III

MASTER CHART- KEY

Sr. Ch – Serum Cholesterol

Sr. TGL – Serum Triglycerides

Sr. HDL – Serum High Density Lipoprotein

Sr. LDL – Serum Low Density Lipoprotein

FBS – Fasting Blood Glucose

HbA1C – Glycosylated Hemoglobin

Sr. Cr – Serum Creatinine

eGFR – Effective Glomerular Filtration Rate

Sr. UA – Serum Uric Acid

EF – Ejection Fraction

HRCT – High Resolution Computed Tomography

ST – Schrimer's Test

WC – Waist Circumference

ANA – Anti Nuclear Antibodies

RF – Rheumatoid Factor

TSH – Thyroid Stimulating Hormone

TPO – Anti Thyroid Peroxidase antibodies

Sr. Bl – Serum Bilirubin

ALT – Alanine Amino Transferase

ESR – Erythrocyte Sedimentation Rate

NCS – Nerve Conduction Study

Xry Joint – Xray Joints

ANNEXURE-IV

CONSENT FORM (ENGLISH)

I have come to know that Dr. S.SATISH, Postgraduate in the Department of General Medicine is conducting a study on the topic, titled **"A STUDY ON HIGH PREVALENCE OF METABOLIC ALTERATIONS (DYSLIPIDEMIA, DIABETES MELLITUS, HYPERURICEMIA) IN PATIENTS WITH PRIMARY SJOGREN'S SYNDROME"**

I understand that I will not have to suffer any harmful consequences as a result of the study nor will I have any financial constraints. It is understood that blood will be collected from me/bone marrow aspiration or trephine biopsy will be done for me for the purpose of conducting this study. I also understand that I can withdraw myself from this study at any point of time and by doing so it will not affect my treatment in any manner. Understanding all these, I wholeheartedly agree to take part in this study.

Signature

Name of the patient:

Signature

Name of the doctor:

Place:

Date:

ANNEXURE-V

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி :

கோவை அரசு மருத்துவக் கல்லூரி மருத்துவமனையில் மரு.**சதீஸ்** தலைமையில் நடைபெறும் இந்த ஆய்வில் எனது முழுஉடல் மற்றும் **இரத்த பரிசோதனை** செய்து கொள்ள முழு மனதுடன் சம்மதிக்கிறேன். என்னைப் பற்றிய விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன். நான் எந்த நேரத்திலும் ஆய்வில் இருந்து விலக்கிக் கொள்ளும் உரிமை உண்டு என்று அறிவேன்.

இடம் கையொப்பம்/கைரேகை

தேதி